Some Aspects of the Chemistry of Benzodiazoles

A Thesis submitted by
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in support of his candidature for the degree of
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STATEMENT

The work described in this thesis was carried out by the author at Leicester Polytechnic during January 1967 to April 1970.

No part of it is concurrently being submitted for any other degree.

Signed.....

(G. A. JAFFARI)

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SUMMARY

When the mononitroindazoles were methylated under neutral conditions, by methyl iodide in dimethyl sulphoxide and by methyl toluene-p-sulphonate in nitrobenzene, 4-, 6- and 7-nitroindazole gave the 2-methyl isomer as the main product, whereas 5-nitroindazole formed mainly the 1-methyl isomer. Methylation of 4-nitroindazole under acidic conditions, using diazomethane in the presence of boron trifluoride etherate, gave equal amounts of the 1- and 2-methyl isomers; however 6-nitroindazole yielded only the 1-methyl isomer and 5-nitroindazole solely the 2-methyl isomer. The separation of the products was achieved mainly by column chromatography.

The methylation of 6-hydroxyindazole by methyl iodide and dimethyl sulphate under alkaline conditions and by diazomethane under acidic and neutral conditions, gave 6-methoxyindazole and 6-methoxy-2-methylindazole. It was found that the addition of nitrobenzene doubled the yield of 6-methoxyindazole in the Dennler Frasca synthesis.

A convenient synthesis of 1, 2-dimethylindazoline, via 1, 2-dimethyl-3-iodoindazolium iodide, was accomplished in good yield.

6-Nitroindazole hydroformylated at 20° yielded 1-hydroxymethyl-6-nitroindazole, whilst at 60° it gave solely 1-methoxymethyl-6-nitroindazole. Cyanoethylation gave both the 1- and 2- isomers.

When 3-methylindazole was reacted with dichlorocarbene under neutral and basic conditions, no ring expansion occurred, but under the latter conditions a small amount of tri (3-methyl-1-indazolyl) methane was formed.

3-Phenyl-2-hydroxyindazole heated in xylene gave benzophenone and 3-phenylindazole (Section 1).

The position of quaternisation of 1, 2, 3-benzothiadiazole has been established by a direct synthesis of 3-ethyl-1, 2, 3-benzothiadiazolium bromide. 2-Aminophenylbenzyl sulphide was converted to N-ethyl-2-hydrazinophenylbenzyl sulphide by acetylation, reduction, nitrosylation and finally reduction with lithium aluminium hydride. This hydrazine was ring closed to give the quaternary salt (Section II).

Aniline and certain aromatic primary amines with an o or p electron donating group, were oxidised by ethereal monochloramine under mild conditions to give the corresponding azobenzenes, often as both cis- and trans- isomers.

Under similar conditions, benzyl alcohol, diphenylmethanol and cyclohexanol gave the respective carbonyl compounds (Section III).

CONTENTS

SECTION III

INTRODUCTION

DISCUSSION OF RESULTS

EXPERIMENTAL

SECTION I

INTRODUCTION

AIMS OF THE WORK

The first object of the present work was to study the pattern of alkylation of mononitroindazoles and hydroxyindazoles under aprotic conditions, and to find out the best reaction conditions making use of the following alkylating reagents, which as yet have not been employed for alkylation of indazoles. Dimethyl sulphoxide is regarded as a favourable solvent for alkylation reactions, as it cuts down the reaction time and usually gives an increased yield of alkylated products. It was thought that the use of alkyl halide in dimethyl sulphoxide for the alkylation of mononitroindazoles might prove to be a convenient alkylating agent and result in a high yield of alkylated mononitroindazoles. Alkyl toluene-p-sulphonates in nitrobenzene might also serve the same purpose. Also they should be efficient alkylating agents of wide application. Higher alkyl halides and alkyl toluene-p-sulphonates are easily available. The readily available dialkyl sulphates are restricted to the methyl and ethyl homologues, as very few higher dialkyl sulphates have been made. In those cases where the alkyl toluene-p-sulphonates are not sufficiently reactive, alkyl 2, 4-dinitrobenzene-sulphonates might be employed. Secondly the isomers could be separated from the mixtures more effectively and quantitatively by the modern chromatographic techniques (column, g.l.c. and t.l.c.).

For the methylation of mononitroindazoles previous workers have employed mainly dimethyl sulphate in alkali and occasionally methyl iodide and sodium methoxide (protic conditions). The isomer ratios have varied and in some of the early work yields were not quoted. Furthermore in this early work the separation of 1-isomer from the 2-isomer was achieved by classical methods, for example fractional crystallization, fractional distillation, and difference in acid

solubility of the two isomers.

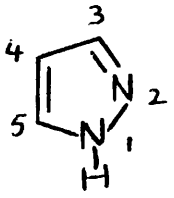
The second object was to establish a convenient route to N-substituted indazolines as these are possibly of pharmaceutical interest. These compounds can not be obtained by direct reduction of indazoles; the aromatic ring and not the pyrazole ring is reduced by hydrogen and catalyst. One compound of this class 1, 2-dimethylindazoline has been obtained by König and Huisgen by the ring closure of a substituted methylhydrazine via a benzyne intermediate.

The third idea was to investigate the mechanism of the thermal rearrangement and decomposition of 2-hydroxy-3-phenylindazole to benzophenone.

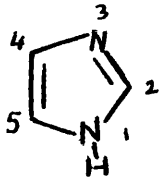
The final aim was to see whether the heterocyclic ring of 3-methylindazole will undergo ring expension reactions with dichlorocarbene.

BENZODIAZOLES

Diazoles contain two nitrogen atoms in a five membered ring, and two isomeric forms are possible, 1,2-diazole (pyrazole) (I) and 1,3-diazole (imidazole) (II).



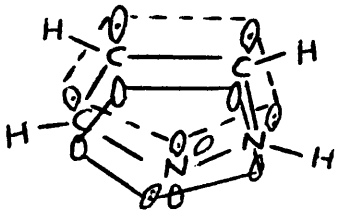
(I)



(II)

They can be regarded as derivatives of pyrrole in which one of the methine groups (=CH-) has been replaced by a nitrogen atom. In

considering the molecular orbital diagram of these substances each of the three carbon atoms contribute one pz-electron to the molecular orbital, while the azole nitrogen donates one p-electron, and the second nitrogen a lone pair of electrons to complete the aromatic sextet as shown in (III) and (IV). Thus one nitrogen is of the pyrrole type and the other of the pyridine type.



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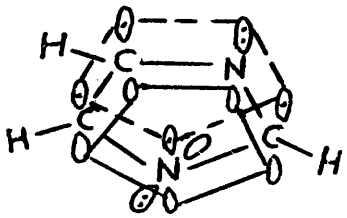
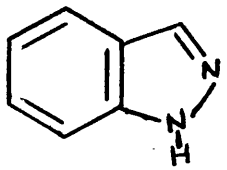


(IV)

The fusion of a benzene ring at position 4 and 5 in the structures (I) and (II) would result in the formation of the benzodiazoles, benzopyrazole (V) and benzimidazole (VI).



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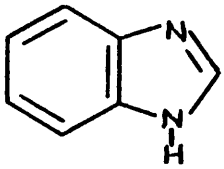


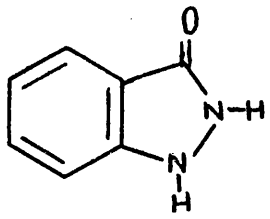
(VI)

Molecular orbital considerations of the benzodiazole system show that each of the seven carbon atoms contributes one pz-electron, whereas the azole nitrogen contributes one pz-electron and the second nitrogen a lone pair of electrons. Thus they are ten π electron systems like naphthalene. A comparison of chemical properties of benzopyrazole (V) with naphthalene has been described by Fries[1]. The name indazole was given by Fischer and Kuzel to the benzopyrazole system by analogy with indole.

In 1956 Elderfield[2] reviewed the chemistry of indazoles. Then

Behr[3] in 1967 reviewed their chemistry in more detail. In the following an attempt is made to develop the background of the chemistry of the indazole ring system. Some features of historical importance regarding the structure of indazoles, alkylation reactions of mononitroindazoles and hydroxyindazoles, n.m.r. and u.v. studies of indazoles are described.

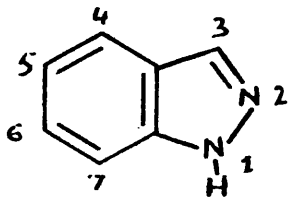
Since the discovery of indazolinone (VII), the first compound containing the indazole ring system, the chemistry of indazoles has been thoroughly studied. This may be due to the easy formation of indazole ring system by ring closure methods.



(VII)

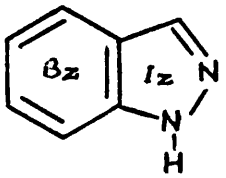
NOMENCLATURE OF INDAZOLES

At the end of the last century 1-substituted indazoles were referred to as isoindazoles and 2-substituted indazoles as simply indazoles. In Chemical Abstracts these have been indexed as 1 H-indazoles for 1-substituted and 2 H-indazoles for 2-substituted indazoles. The numbering of the ring is shown in (VIII).



(VIII)

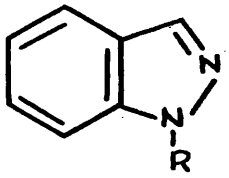
The symbols Bz and Iz have been used by Bamberger[4] and Noelting[5] to indicate the carbocyclic ring and pyrazole ring in indazoles (IX).



(IX)

STRUCTURE OF INDAZOLE

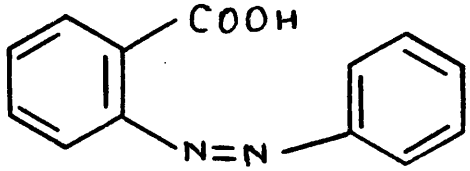
Extensive work has been done to establish the structure of indazole and its 1-and 2-substituted derivatives. Both chemical and physical techniques have been applied to elucidate the structure of these compounds. The following is a brief account of the investigations which have been reported in the literature. Indazole and 1-substituted indazoles can be represented by the conventional structure (X) and this has been generally accepted on the basis of their chemical reactions, ultraviolet measurements and n.m.r. spectra.



(X)

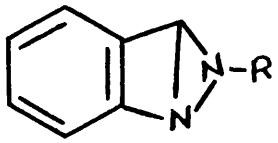
Rousseau and Lindwall[6] supported the structure (X) for indazole and 1-substituted indazole by observing the u.v. spectra of the two which are very similar to one another. Elguero, Fruchier and Jacquier[7] studied the n.m.r. spectra of indazole, 5-nitroindazole, 6-nitroindazole and their 1- and 2- methyl derivatives. They observed a methyl signal at τ5.98 and 5.87 in the 100 Mc/s spectra of 1-methylindazole and 2-methylindazole respectively and from this slight difference it was difficult to decide conclusively between the two isomers nor did it help to establish the structure of the 2-substituted derivatives of the indazoles. 2-Substituted indazoles are difficult to represent by a single formula. From time to time different structural formulae have

been advanced to account for the observed properties of 2-substituted indazoles. It was noticed that the carbocyclic nucleus of 2-substituted indazoles underwent normal aromatic substitution reactions. Also the 2-substituted indazoles were not intensely coloured compounds, which suggested aromatic rather than quinonoid character. It was observed that the oxidation of 2-phenylindazole gave azobenzene-2-carboxylic acid[8] (XI).



(XI)

Therefore a tricyclic formula (XII) was proposed to account for the aromatic character of 2-substituted indazole.

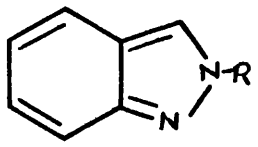


(XII)

Auwers and Düesberg[9] on the basis of molecular refractivity and dispersion measurements of various substituted indazoles also advocated the structure (XII) for 2-substituted indazoles.

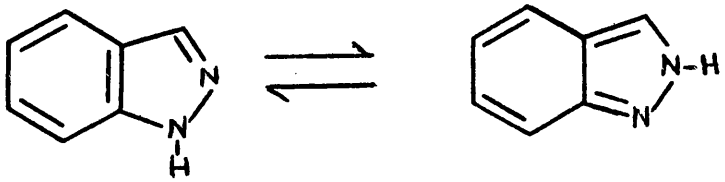
However this structure (XII) encountered serious objections from other workers and now is only of historical importance.

The specific exaltations of 1-substituted indazoles are lower than those of 2-substituted indazoles. On the basis of this difference, Auwers, Hügel and Ungemach[10] suggested the quinonoid structure (XIII) should be applied to the 2-substituted indazoles.



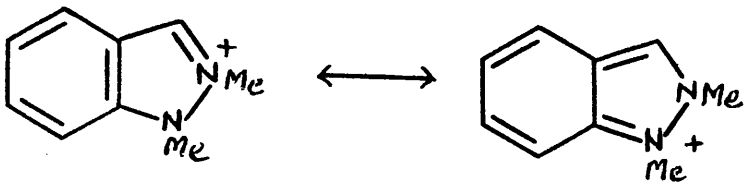
(XIII)

To account for the properties of indazole, it was proposed that indazole could best be represented by a tautomeric equilibrium (XIV).



(XIV)

The mobile imino hydrogen in the tautomeric equilibrium would result in isomerism. This was supported by the existence of two forms of 3-phenylindazole[11-13], which are interconvertible under various conditions. Similar interconversion of two forms has been observed with 5-chloroindazole[14], 5-bromoindazole[14], and 5-methyl-7-acetylaminoindazole[15]. Barclay et al[16] found that bromine is replaced by piperidine in appreciable amount only from 3-bromo-5-nitro-2-methylindazole, whereas bromine in 3-bromo-4-nitro, 3-bromo-6-nitroindazole and their 1-and 2-substituted derivatives is practically non-replaceable by piperidine. Thus Barclay et al[16] have suggested that the quinonoid form is the important resonance contributor in the equilibrium (XIV). Further it has been found by Auwers et al[12] that the treatment of either 1-methylindazole or 2-methylindazole with methyl iodide yields the same indazolium salt. Thus 1, 2-dimethylindazolium cation can be represented as a resonance hybrid with the two structures (XV) and (XVI).



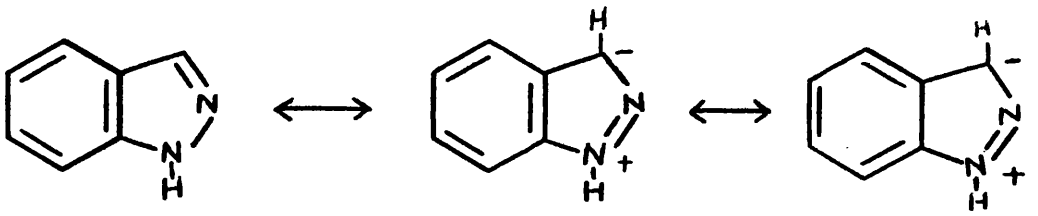
(XV) (XVI)

SUBSTITUTION REACTIONS OF INDAZOLES

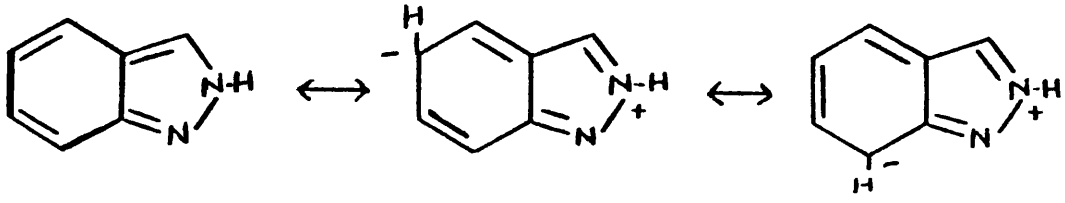
The reactions of indazoles can be studied under two headings (A) C-substitution, involving carbon atoms of both carbocyclic ring and pyrazole ring. (B) N-substitution due to nitrogen atoms of pyrazole ring.

(A) C-Substitution.-

Due to the aromatic character, indazole and its derivatives undergo the usual aromatic substitution reactions such as halogenation, nitration, sulphonation etc. Halogenation has been studied in detail, but little work has been done on other types of substitution. The most facile positions of electrophilic substitution in indazoles appear to be 3, 5, and 7. From a valence bond point of view, contributing structures (XVII) - (XXII) can be written.



(XVII) (XVIII) (XIX)



(XX) (XXI) (XXII)

(i) Halogenation.

In the indazoles substitution by halogens takes place most readily at positions 3, 5, and 7. Chlorination and bromination have been performed usually in protic medium (water and acetic acid) or by the use of sodium hypohalite solutions. Iodination does not occur directly (except with iodine in the presence of sodium hypoiodite). Auwers et al[17] made 3-iodoindazole by the reaction of iodine with silver indazole. Similar treatment of silver indazole with bromine gave 3-bromoindazole[17]. Indazoles unsubstituted on the nitrogen underwent halogenation in the 3-position preferentially, however because the 5-position was nearly as active as the 3-position a limited quantity of halogen was used to check the formation 3, 5-dihalogenated indazoles. Auwers and Lange[17] have shown that the presence of a methyl group on one of the nitrogen atoms of indazole attracted halogen into its neighbourhood and increased the ease of halogenation, so that the 3-bromo derivative can be obtained from 2-methylindazole and a 3, 5, 7-tribromo compound from 1-methylindazole.

(ii) Nitration.

Very little work has been done on the nitration of indazole and its derivatives. Nitro derivatives are obtained by ring closure reactions. However the reaction of indazole with fuming nitric acid affords a nearly quantitative yield of 5-nitroindazole[18]. Further nitration yields the 5, 6-dinitroindazole[18], which is also obtained in excellent yield by nitration of 6-nitroindazole . 3-Methylindazole on nitration gave 3-methyl-5-nitroindazole[19]. Similarly 7-bromo-6-hydroxy-indazole was nitrated at the 5-position[20].

(B) N-Substitution.-

Indazole is basic; its indazolium anion has been reported[21]

to have pKa $1.3^{\pm}$ 0.2. This anion is a resonance hybrid (XXIII) in which the electron density is concentrated at either N-1 or N-2, and hence two N-substituted isomers

(XXIII)

are frequently formed.

(a) N-Alkylation.

(i) Indazoles

Alkylation of indazoles has been carried out by the following procedures.

1. Heating the indazole with alkyl halide, with or without a solvent.
2. Heating the silver indazole with alkyl halide.
3. Warming the indazole with alkyl halide in presence of sodium alkoxide.
4. Warming the indazole with dialkyl sulphate in aqueous alkali.

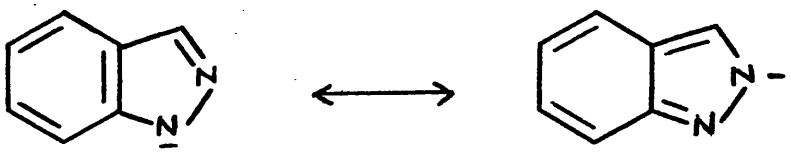
The usual product is a mixture of the 1- and 2-alkylindazoles. The alkylation reactions of indazole have been extensively studied in the past. The major work has been done by Auwers and his co-workers[9,18,22-26] and the results obtained by them vary so much that no generalization can be made. However, the factors which affect the ratio of two isomers are the nature of alkyl halide, the reaction temperature, and the procedure used. This can be seen from the following account of some of the more important results. It appeared that in alkaline solutions, both isomers resulted in nearly equal amounts. However C. Paal[8] observed that isopropyl, allyl and benzyl bromide produced only the N-1 derivatives. Heating indazole with allyl bromide resulted in 2-substitution.[22]

Auwers[22] reported that with silver indazole only methyl

iodide, allyl iodide and benzyl iodide reacted with sufficient velocity at room temperature; methyl iodide gave exclusively the 2-isomer, the other two iodides only the 1-derivative. Experiments with ethyl iodide showed that increasing the temperature, increased the tendency towards the formation of the 1-alkylindazole; the ratio of 1- to 2-isomer was about 1:1 at 30°, 10:1 at 40° and 1:0 at 50°.

Similarly methyl iodide at 50° no longer gave the 2-derivative exclusively, but also about 33% of the 1-derivative. Propyl iodide at 100° gave a 2:1 ratio of the 1- and 2-derivatives. iso-Amyl iodide at 100° yielded, in small amount, the 1-derivative exclusively. These results show that the formation of 1-isomer is favoured thermodynamically.

Auwers et al[34] considered that alkylation reactions of indazoles were comprehensible if they were regarded partly as substitution, and partly as addition. In the first case the hydrogen or sodium bound to the nitrogen was directly replaced by the alkyl group of the alkyl halide; in the second case alkyl halide added to the tertiary nitrogen and then the hydrogen halide or sodium halide was evolved. Also that the reaction of silver indazole with alkyl halide could be understood if the intermediate formation of anions (XXIV) and (XXV) was assumed to be similar to the keto-enols and different affinity characteristics of the alkyl groups taken into account.



(XXIV) (XXV)

(ii) Nitroindazoles

Mononitroindazoles, having a nitro group in the benzene ring have the properties usually attributed to aromatic nitro compounds,

namely they are readily reduced to the amino compounds. The presence of a nitro group in the carbocyclic ring of the indazole nucleus imparts extra acidity to the imino group. They have been reported to have pKa values[3] as shown in Table 1. No indazole with a nitro group in the pyrazole ring has been described in the literature.

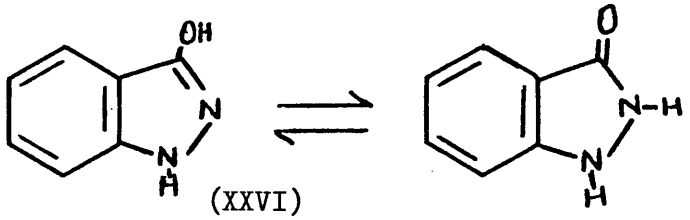
Table 1

Parent compound	pKa values
Indazole	$1.3^{+}_{-}0.2$
7-Nitroindazole	3.18
6-Nitroindazole	4.00
5-Nitroindazole	5.25

The literature on the alkylation of the nitroindazoles is somewhat confused. The alkylating conditions and the products of reaction reported in the literature are summarised in Table 2. Like indazole, the nitroindazoles also form N-1 alkylated or N-2 alkylated products.

(iii) Hydroxyindazoles

Alkylation on the hydroxyindazoles has been little studied, particularly with benz-ring substituted hydroxyindazoles. A survey of the literature did not show any direct method for the conversion of benz-substituted hydroxyindazoles into the corresponding methoxy derivatives. Some work has been done on alkylation of the hetero ring substituted 3-hydroxyindazole (indazolinone) (XXVI).



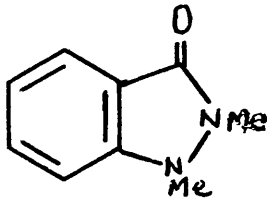
(XXVI)

Indazolinone with methyl iodide in potassium hydroxide-methanol[35] has been reported to yield 1-methylindazolone (31%), whereas 3-methoxyindazole is obtained by the reaction of indazolinone with diazomethane in ether-methanol[36]. 1-Methyl-3-hydroxyindazole with diazomethane in

Table 2

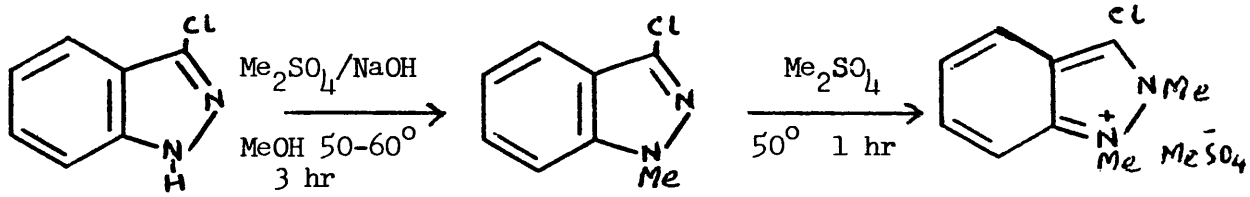
Indazole	Alkylating conditions	1-Methyl isomer		2-Methyl isomer		Literature reference
		(%)	m.p.	(%)	m.p.	
4-Nitro	MeI/KOH-MeOH for 4 hr	20	136°	7	98°	16
	MeI at 100° → 24 hr	minor amt.	135-36°	major amt.	101-3°	27
	Me_2SO_4/KOH -, 60°	-	-	yield not stated	81-2°	5
	Me_2SO_4/KOH -, 50°	9.5	139°	12.6	101°	28
5-Nitro	Me_2SO_4 in alkali	-	-	yield not stated	129°	5
	Me_2SO_4/alkali	yield not given	129°		163°	29
	Me_2SO_4/KOH -, 60-80°, 15 mts	70	109°	--	-	30
	Me_2SO_4/NaOH, 65°, 2 hrs	25	129°	62	163°	31
	CH_2N_2 0°, 5 days	20	129°	42	163°	31
6-Nitro	CH_2N_2 0°, 5 days	22.5	125°	54	160°	31
	Me_2SO_4/(2N alkali) 1 hr room temperature	-	-	50	159°	32
	MeI/KOH	1 part	125°	3 parts	160°	16
	Me_2SO_4/32% NaOH, 60-65°	not stated	122°	-	158°	33
	MeI (excess), 100°, 4hr in sealed tube	minor amt.	108°	major amt.	159°	45
	MeI/MeONa, boiling MeOH	major amt.	108°	minor amt.	159°	45
	Alk. Me_2SO_4/shaking	-	-	not stated	159°	45
	Me_2SO_4/alkali → 100°	40	116-118°	43	159°	46
7-Nitro	Me_2SO_4/32% NaOH, 60-65°, 2hr	53	98°	49	143°	33

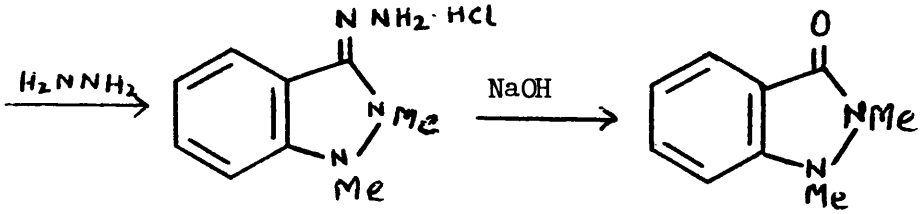
ether-methanol[37] gives mainly 1-methyl-3-methoxyindazole and a small amount of 1, 2-dimethylindazolin -3-one(XXVII).



(XXVII)

This compound (XXVII) is also reported[38] to be formed as shown below.



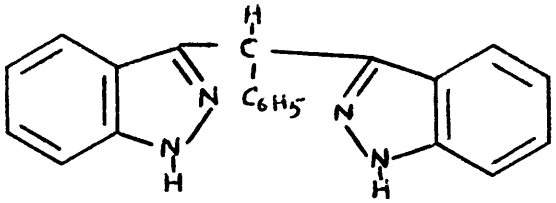


(XXVII)

(b) Hydroformylation.

The reactions of indazole and nitroindazoles with aldehydes have been little studied. The following two instances of reactions of indazoles with aldehydes have appeared in the literature.

(1) Fischer and Seufert have condensed indazole with benzaldehyde in presence of zinc chloride and obtained a substance, which they regarded as benzalindazole.[39] In Beilstein's[40] handbook it is named 3,3'-benzal-di-indazole and given structure (XXVIII).



(XXVIII)

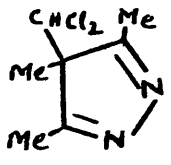
(2) In the hands of Pozharskii et al[41] indazole failed to react with formaldehyde in neutral medium but it reacted under acidic conditions at room temperature to give 1-hydroxymethyl-indazole (67%). No 2-hydroxymethylindazole was obtained. These authors found that 6-nitroindazole in an acidic medium reacted with formaldehyde to give only 1-hydroxymethyl-6-nitroindazole (80%). This behaviour of indazole and 6-nitroindazole towards hydroformylation is in contrast to the alkylation of indazole and nitroindazoles, where a mixture of two isomers is frequently obtained.

(c) Cyanoethylation.

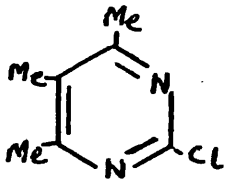
The reaction of indazole and nitroindazoles with acrylonitrile has been studied only in the last twenty years. Rousseau and Lindwall[6] condensed indazole with acrylonitrile in butanol at 40° for two days and obtained a substance which they called 1-(2'-cyanoethylindazole) (89%). This compound was also obtained by Jao Êrh-Ch'ang and M. N. Shchukina[43] in high yield (86%) from the reaction of indazole with acrylonitrile at 42-43° for three days. They named it β-(indazyl-1)-propio-nitrile. Under these reaction conditions 6-nitroindazole has also been shown to give β-(6-nitro-indazyl-1)-propionitrile (96%). Thus both of these groups of workers reported the formation of only N-1 cyanoethylated derivatives of indazole and 6-nitroindazole respectively. These results are contra to the general tendency of indazole and nitroindazoles on alkylation when both N-1 and N-2 isomers are formed.

(d) Attempted ring expansion

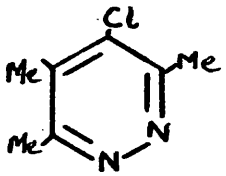
Jones[44] has shown that various pyrroles, imidazoles and pyrazoles react with dichlorocarbene, both under basic and neutral conditions. The reaction of dichlorocarbene with pyrroles gives ring expanded products and pyrrolenines. 2, 4, 5-Trimethylimidazole with dichlorocarbene in both basic and neutral conditions gave only the ring expanded product, 5-chloro-2, 4, 6-trimethylpyrimidine in very low yield. The reaction of 3, 4, 5-trimethylpyrazole with dichlorocarbene under basic conditions gave 4-dichloromethyl-3, 4, 5-trimethylpyrazolenine (XXIX), as the major product, and a little 1-ethyl-3, 4, 5-trimethylpyrazole. No ring expanded compound was formed, whereas in neutral aprotic conditions dichlorocarbene reacted with 3, 4, 5-trimethylpyrazole to give 2-chloro-4, 5, 6-trimethyl-pyrimidine (XXX) (0.4%), and a compound thought to be 4-chloro-3, 5, 6-trimethylpyridazine (XXXI) (0.5%), both as a result of ring expansion. In addition 1-trichlorovinyl-3, 4, 5-trimethylpyrazole (XXXII) (0.1%) and tri (3, 4, 5-trimethyl-1-pyrazolyl) methane (XXXIII) (3.1%) were formed via the N-substituted products of the parent pyrazole.



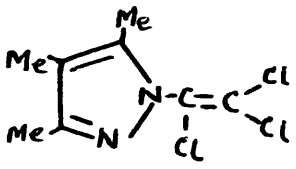
(XXIX)



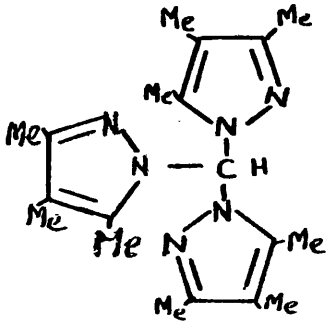
(XXX)



(XXXI)



(XXXII)



(XXXIII)

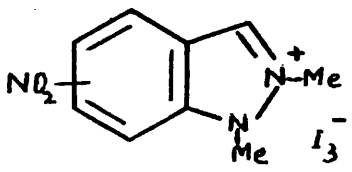
DISCUSSION OF RESULTS

METHYLATION OF NITROINDAZOLES

In the present work Noelting's method was used for the preparation of mononitroindazoles. For example 5-nitroindazole was prepared by diazotization of 2-amino-5-nitro-toluene with sodium nitrite in acetic acid, followed by ring closure, and subsequently the methylation of these mononitroindazoles was studied as described below.

By Methyl Iodide in Dimethyl Sulphoxide.-

4-, 5-, 6-, and 7-Nitroindazole when treated with methyl iodide in dimethyl sulphoxide at 70°, gave the 2-methyl isomer as the main product in each case, except for 5-nitroindazole, where the 1-methyl isomer was formed predominantly. Quaternary periodides were also isolated in small amounts from these reactions (Table 3). They were formed as side products by association of molecular iodine with the quaternary salts. The elemental analysis of the periodides suggest the molecular formula $C_9H_{10}N_3O_2I_3$ corresponding to structure (XXXIV). Some free iodine vapours were evolved when these periodides were boiled with methanol.



(XXXIV)

By Methyl Toluene-p-sulphonate in Nitrobenzene.-

Mononitroindazoles reacted with methyl toluene-p-sulphonate

in nitrobenzene at 90° and yielded the 2-methyl isomer as the main product, except for 5-nitroindazole where the 1-isomer predominated as in the methylation of mononitroindazoles by methyl iodide and dimethyl sulphoxide. With methyl toluene-p-sulphonate unreacted starting material was isolated instead of quaternary periodides (Table 3).

By Diazomethane - Boron Trifluoride Etherate.-

4-, 5-, and 6-Nitroindazole reacted with diazomethane in the presence of boron trifluoride etherate at 18°. 4-Nitroindazole gave equal amounts of the 1- and 2-methyl isomers, 5-nitroindazole gave exclusively the 2-methyl isomer (50%) and 6-nitroindazole yielded the 1-methyl isomer (75%) (Table 3).

By Methyl Iodide in Sodium Methoxide.-

7-Nitroindazole reacted with methyl iodide in sodium methoxide at 60° and yielded 1- and 2-methyl isomers in the proportion of 1:4 respectively, but indazole under these conditions gave 1- and 2-methylindazole in the ratio of 3:1 respectively.

Possible Mechanism.-

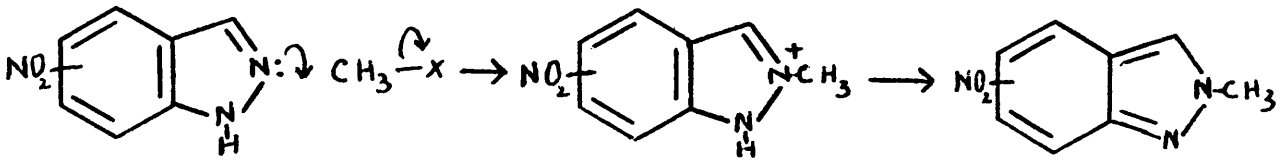
The results obtained in this work during the study of methylation reactions of mononitroindazole (Table 4) suggest that the predominant formation of 1- or 2-methyl isomers depends perhaps on the neutral basic or acidic conditions under which the methylation is performed. This is also supported by the results obtained by the previous workers which are summarised in Table 5. Under neutral conditions, the neutral indazole molecule is involved and

Table 3

METHYLATION OF MONONITROINDAZOLES

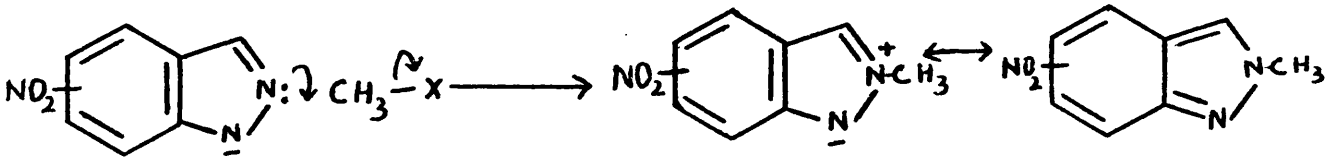
Alkylating conditions	4-Nitroindazole			5-Nitroindazole			6-Nitroindazole			7-Nitroindazole		
	1-Me (%)	2-Me (%)	Periodide (%)	1-Me (%)	2-Me (%)	Periodide (%)	1-Me (%)	2-Me (%)	Periodide (%)	1-Me (%)	2-Me (%)	Periodide (%)
CH_3I in DMSO at 70°	-	50	20	50	10	17	10	50	17	-	30	50*
(MTS) in $PhNO_2$ at 90°	-	60	20*	60	10	30*	-	50	25*	-	40	50*
CH_2N_2 - (BFE) at 18°	50	50	-	-	50	-	75	-	-	-	-	-
CH_3I - CH_3ONa	-	-	-	-	-	-	-	-	-	14	56	-

(MTS) Methyl toluene-p-sulphonate
(BFE) Boron trifluoride etherate
* Unreacted starting material

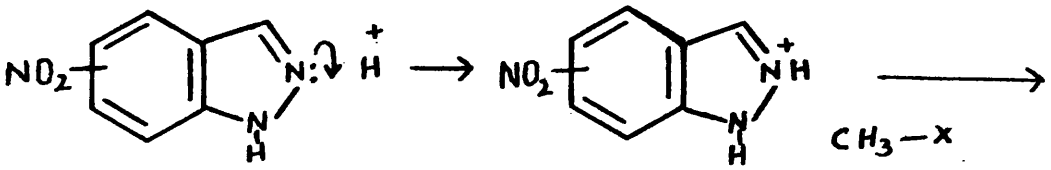


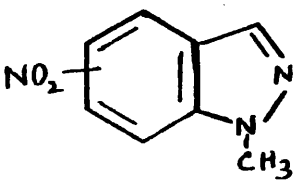
where (X = I, or CH_3-C_6H_4-SO_3)

in presence of base (i.e. under basic conditions) indazolyl anion could react with methylating reagent and could give the 2-methyl isomer predominantly by a concerted mechanism:

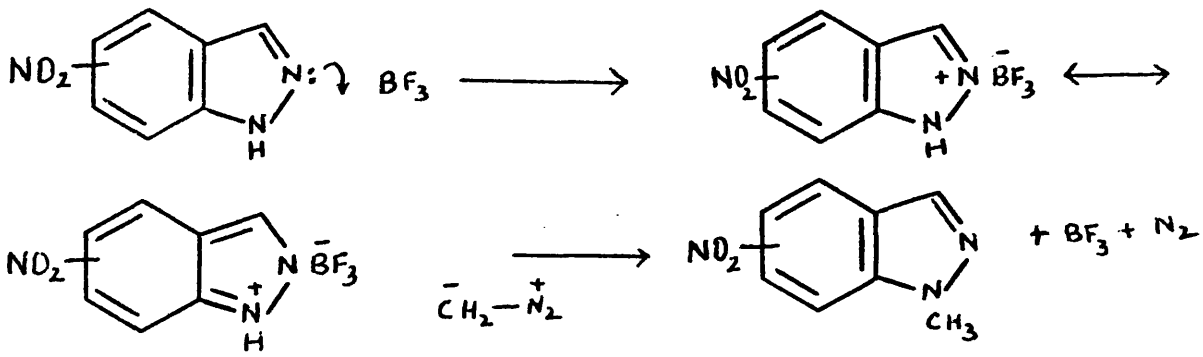


whereas under acidic conditions the protonated indazolium cation is formed and should favour the formation of 1-isomer.





The methylation of mononitroindazoles by diazomethane in the presence of Lewis acid involved perhaps the formation of an N-boron complex which reacted with diazomethane to give the N-1 methylated products.



A similar mechanism has been proposed for the O-methylation of alcohols by diazomethane in the presence of Lewis acid.[53]

$$ROH \xrightarrow{BF_3} R-\overset{+}{\underset{H}{O}}-\bar{B}F_3 \xrightarrow{CH_2N_2} ROCH_3$$

The above mechanisms are supported by a comparative study of the results obtained by the comparative results shown in Table 5 which is a summary of Table 2 (p.13).

Table 4

Methylating reagent used and conditions	Formation of predominant isomer			
	4-Nitro	5-Nitro	6-Nitro	7-Nitro
CH_3I- DMSO (Neutral)	2	1	2	2
$MeO.SO_2Ar$(Neutral)	2	1	2	2
CH_2N_2 - BF_3 (Acidic)	equal	2	1	-
CH_3I - CH_3ONa (basic)	-	-	-	2

It may be stated here that Auwers and Düesberg[9] had formulated the rule that alkylation of indazole by alkyl iodides in presence of sodium alkoxides, takes place mainly in the 1-position. Exceptions to this rule are known, for example, the methylation of methyl indazole-3-carboxylate using either methyl iodide and sodium methoxide, or dimethyl sulphate and sodium hydroxide, leads to the formation of 2-methylindazole-3-carboxylate[52]. Barclay, Campbell and Dodds[16] found other exceptions in the methylation of 6-nitroindazole and 3-bromo-6-nitroindazole. Davies[33] studied the methylation of 6- and 7-nitroindazole and also found exceptions in these cases. Kamel et al[31] have reported the formation of 1- and 2-isomers in the proportion of 1:2.5 when 5-nitroindazole is methylated by dimethyl sulphate in sodium hydroxide.

Table 5

Methylating reagent used and conditions	Formation of predominant isomer			
	4-Nitro	5-Nitro	6-Nitro	7-Nitro
CH_3I - base (Basic)	1	-	2	-
Me_2SO_4 - base (Basic)	2	2	2	1
CH_3I alone (Neutral)	2	-	2	-
CH_2N_2 alone (Neutral)	-	2	2	-

These exceptions to Auwers' rule can possibly be explained on the basis of the generalization which is formulated in this thesis and furthermore it can be applied to explain the formation of exclusively

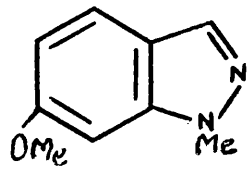
1-isomer in the hydroformylation reactions of mononitroindazoles which will be discussed later.

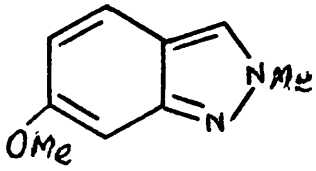
In the present work the separation of the isomers was achieved on neutral alumina columns. It was noticed that the 1-methyl isomer was eluted first in each case. The same order of elution was observed when a known mixture of 1- and 2-methyl-6-nitroindazoles was subjected to g.l.c. on a 5% methyl-silicone gum (E.30) column. This behaviour on elution reflects to some extent the polarity of the two isomers. Thus it seems that the 2-isomers are more polar than the 1-isomers. It was discovered that the best conditions for the quantitative estimation of isomer ratios in a reaction mixture by g.l.c. technique, where the use of 5% E.30 column (made by dispersion of methyl silicone gum on chromosorb P) at a temperature of 250°. In one experiment a known mixture of 1- and 2-methyl-6-nitroindazoles in nitrobenzene was injected into a 5% E.30 column at 250°. The first peak in g.l.c. chromatogram corresponded to nitrobenzene which was followed by the 1- and 2-methyl isomers clearly separated.

METHYLATION OF 6-HYDROXYINDAZOLE

By Methyl Iodide and Sodium Methoxide.-

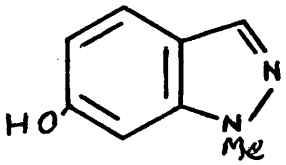
6-Hydroxyindazole reacted with methyl iodide in the presence of sodium methoxide at 70°. The only isolated product was 6-methoxyindazole (25%)(XXXIX) which was separated on an alumina column. Washing of the column with methanol gave a small amount of oily residue which could not be purified and was thought to be the mixture of other methylated products, probably 6-methoxy-1-methylindazole (XXXV) and/or 6-methoxy-2-methylindazole (XXXVI) but not the

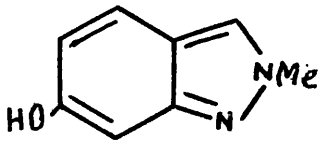




(XXXV) (XXXVI)

1-methyl-6-hydroxyindazole (XXXVII) or 2-methyl-6-hydroxyindazole (XXXVIII),as these are known and have melting points 216° and 169° respectively[46]. The possibility of quaternary compounds cannot be ruled out but seems unlikely in this case because 2 mole methyl iodide and 1 mole 6-hydroxyindazole were used in this reaction. That the oily fraction contained (XXXV) and/or (XXXVI) is supported by the results of methylation by diazomethane which are discussed later (Methylation by diazomethane, P.25).



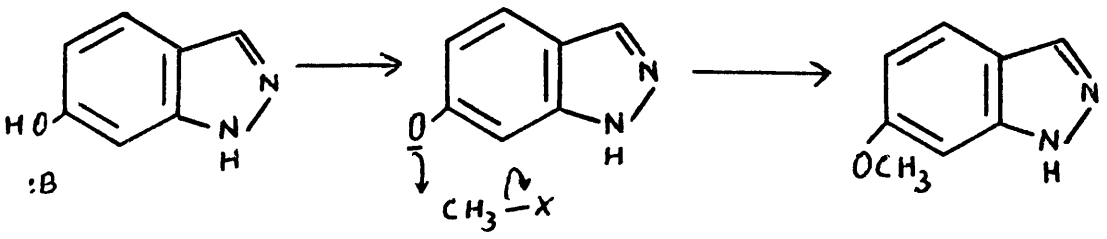


(XXXVII) (XXXVIII)

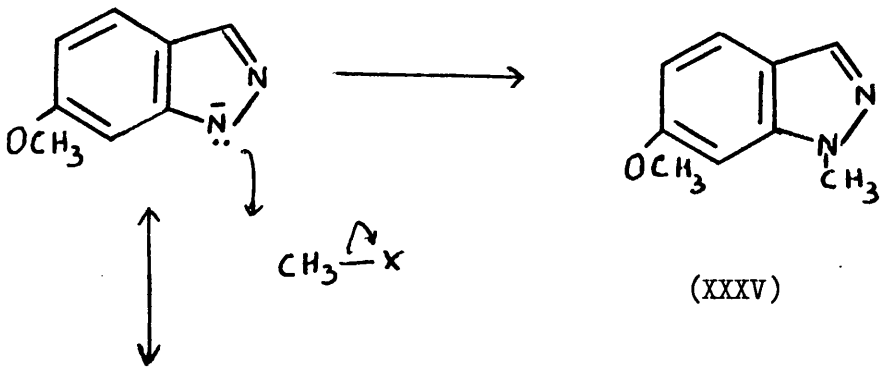
By Dimethyl Sulphate and Alkali.-

Dimethyl sulphate in the presence of aqueous potassium hydroxide (10%) also methylated 6-hydroxyindazole and gave 6-methoxyindazole (40%)(XXXIX). A small amount of oily residue was also obtained in this reaction as in the case of methylation by methyl

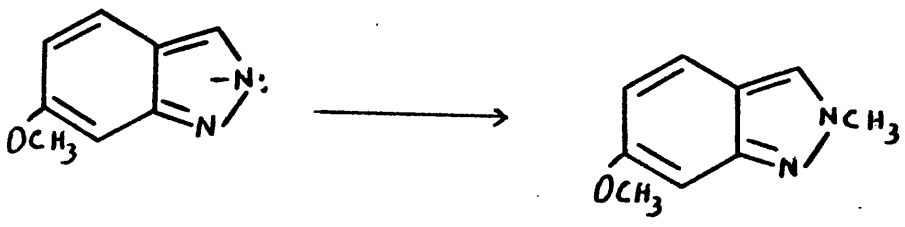
iodide. The nucleophilic reactions of phenols with alkyl halides and alkyl sulphates are well known and follow a simple S_N2 pattern. The same mechanism applies in these reactions. The anion of (XXXIX) will attack a second molecule of CH_3X by an S_N2 mechanism to give (XXXV) and/or (XXXVI).



where (X=I, O-SO_2-OCH_3) (XXXIX)



(XXXV)



(XXXVI)

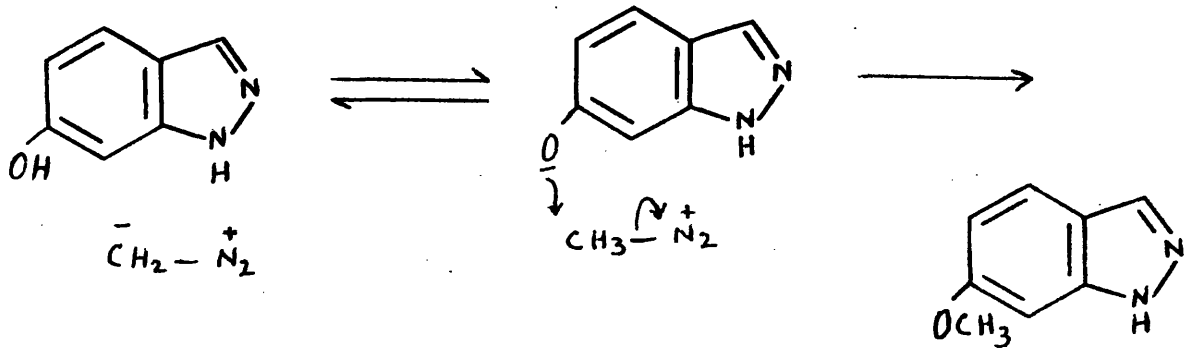
By Diazomethane.-

Diazomethane reacted with 6-hydroxyindazole in the presence of boron trifluoride etherate and without boron trifluoride etherate

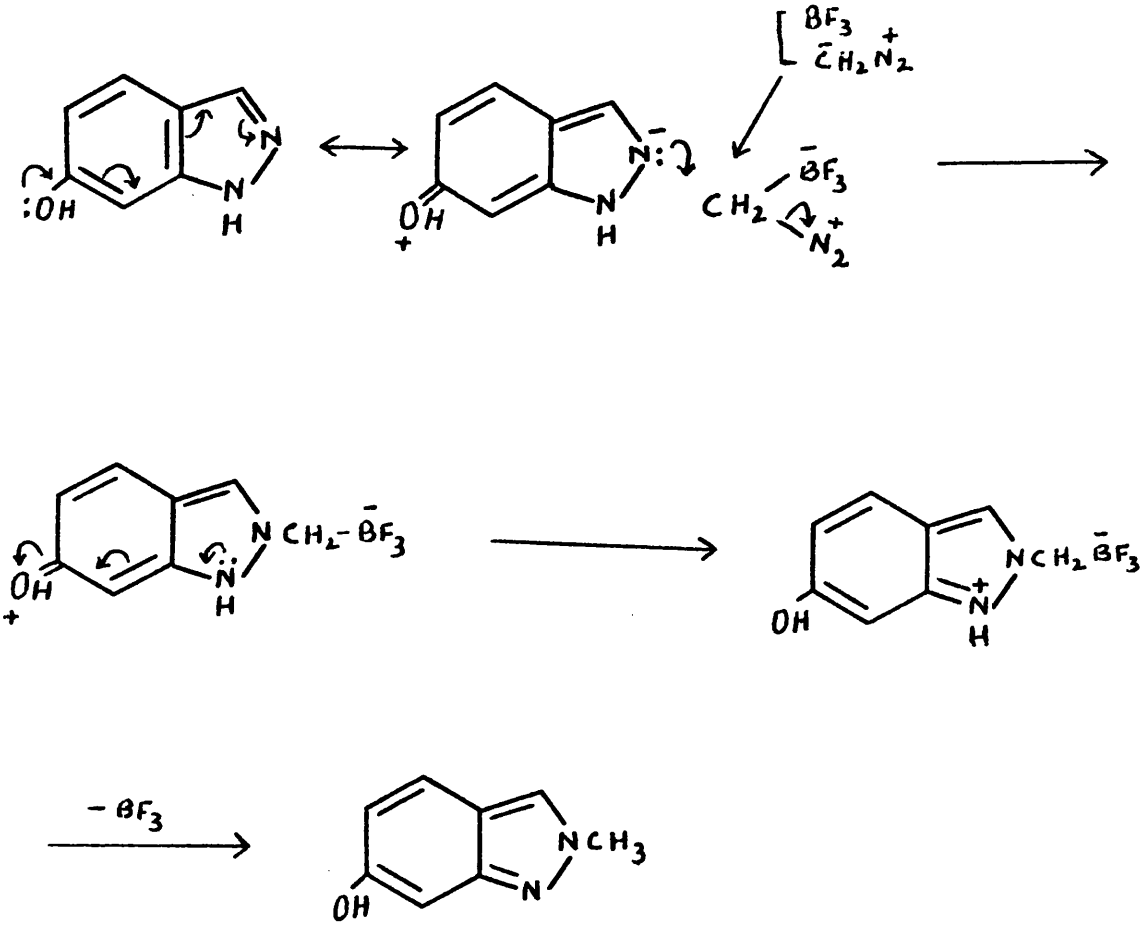
and yielded 6-methoxyindazole (10%) and 2-methyl-6-hydroxyindazole (70%) under both conditions. The authenticity of the 2-methyl-6-hydroxyindazole was checked by analysis and by comparing its m.p. with that in the literature[46]. Furthermore in one experiment on a 100 mg scale 6-methoxyindazole and 2-methyl-6-hydroxyindazole were reacted separately with diazomethane and yielded yellowish oily residues in each case. The i.r. spectra of these oily residues were identical and hence appeared to be 6-methoxy-2-methylindazole (XXXVI), which was also obtained from the reactions with methyl iodide and with dimethyl sulphate. It is surprising that N-methylation takes place predominantly rather than O-methylation especially in absence of catalyst. Usually diazomethane in presence of the Lewis acid catalysts, fluoboric acid[53] and boron trifluoride etherate[54] has been used for O-methylation of alcohols. The formation of a methyldiazonium cation intermediate[53] has been postulated in these O-methylation reactions.

The formation of O-methylated and N-methylated products might be explained according to following schemes:

O-methylation



N-methylation



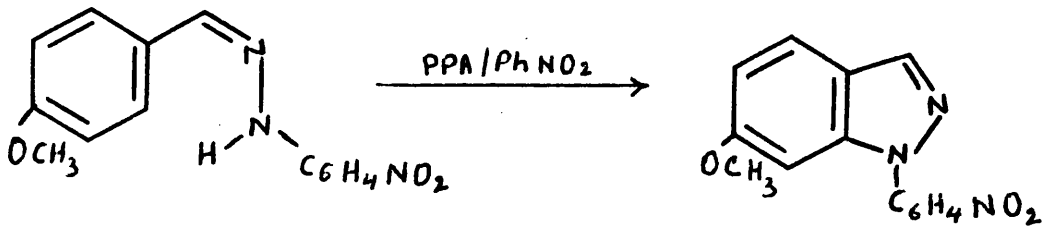
RELATED SYNTHESIS 6-METHOXYINDAZOLE

The authenticity of the product 6-methoxyindazole from each of the methylation reactions of 6-hydroxyindazole was checked by comparison with a sample obtained by the direct synthesis of 6-methoxyindazole from the p-nitrophenylhydrazone of anisaldehyde using polyphosphoric acid[55]. It was found that the addition of nitrobenzene to the reaction mixture increased the yield of 1-p-nitrophenyl-6-methoxyindazole (XL) from 25% as reported[56] to 54%.

(i) 1-p-Nitrophenyl-6-methoxyindazole.-

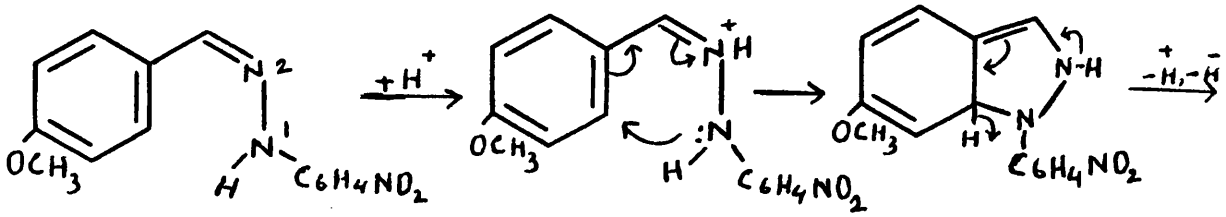
The p-nitrophenylhydrazone of anisaldehyde when heated with

polyphosphoric acid and nitrobenzene ring closed to give (XL).

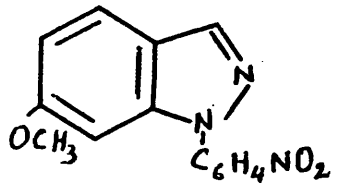


(XL)

The formation of (XL) perhaps involved, initially protonation of N-2 and then nucleophilic attack by N-1 atom of the hydrazone group on the ortho position of the aromatic ring of the ketonic or aldehydic moiety as shown below: (XLI) - (XLIII)



(XLI) (XLII) (XLIII)



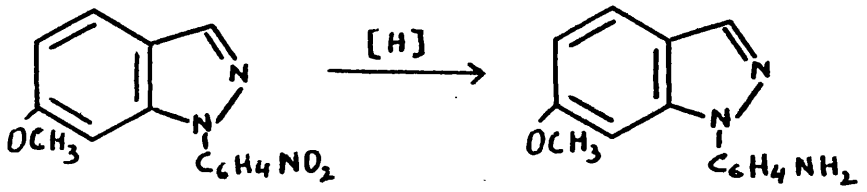
(XL)

This mechanism is similar to the postulated[55, 56] mechanism for the

formation of indazoles. Indazoles are formed[55-57] when the p-nitrophenylhydrazones of several acetophenones[55,56], benzaldehydes[56], benzophenones[56] and acetylated aromatic hydrocarbons[57] are treated with polyphosphoric acid at an elevated temperature.

(ii) 1-p-Aminophenyl-6-methoxyindazole.-

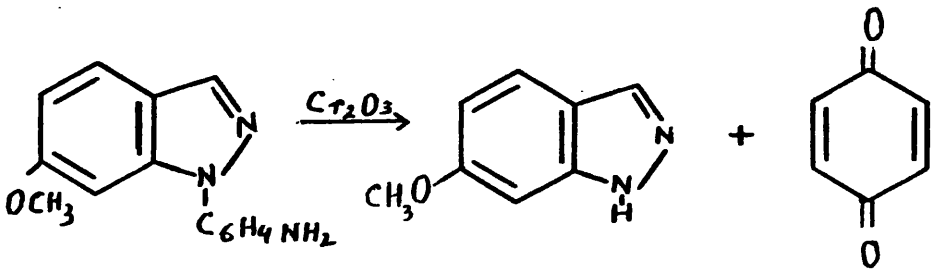
1-p-Nitrophenyl-6-methoxyindazole (XL) was reduced by stannous chloride and hydrochloric acid and yielded, 1-p-aminophenyl-6-methoxyindazole (XLIV)(57%). The structure (XLIV) was supported by its infra red spectrum, which showed two peaks at 3420 and 3340 cm^{-1} due to the $-NH_2$ group and by elemental analysis.



(XL) (XLIV)

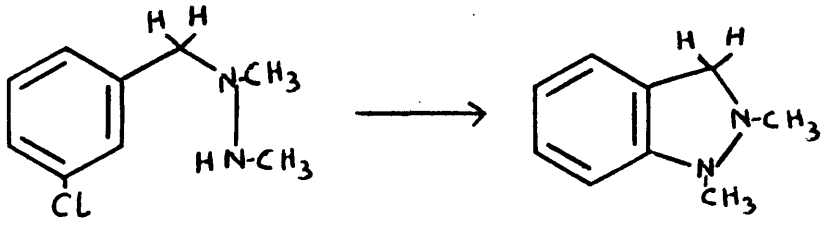
(iii) 6-Methoxyindazole.-

The compound (XLIV) was cleaved by chromic acid and yielded 6-methoxyindazole (17%) m.p. 122-24° identical with the product from the previous methylation reactions of 6-hydroxyindazole.



SYNTHESIS OF 1, 2-DIMETHYLINDAZOLINE

The pyrazole ring reduced indazoles cannot be prepared by the reduction of indazole; the aromatic ring and not the pyrazole ring is reduced. These ar-reduced indazoles are known to possess analgesic and antipyretic properties and are of pharmaceutical interest. König and Huisgen[51] have reported the formation of 1, 2-dimethyl-indazoline (XLV) in 67% yield by the action of phenyl-lithium on 1, 2-dimethyl-1-(3'-chlorobenzyl) hydrazine. This reaction involves a benzyne intermediate.

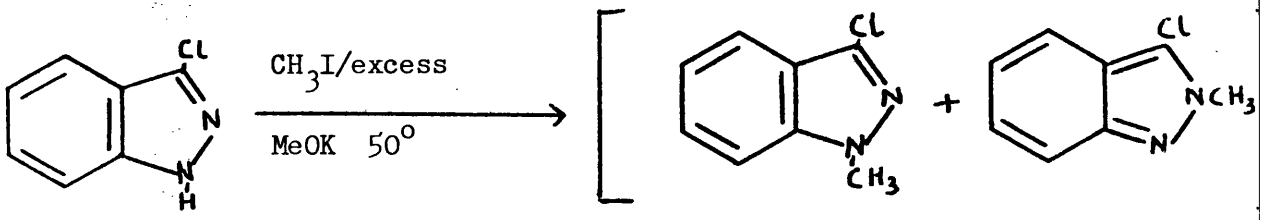


(XLV)

In the present work indazoline (XLV) was synthesised by an unambiguous route starting with the readily available 3-chloroindazole. This involved methylation, followed by quaternisation, hydrolysis and reduction.

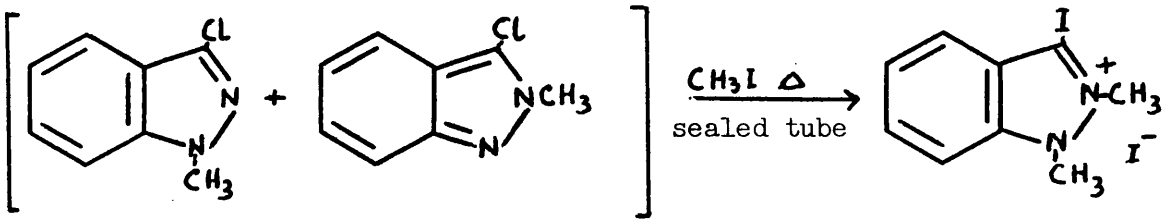
(i) 1- and 2-Methyl-3-chloroindazole.-

3-chloroindazole reacted with methyl iodide in concentrated methanolic potash solution and yielded a mixture of 1- and 2-methyl-3-chloroindazole. No attempt was made to separate the mixture into its components. The authenticity of the product was checked by analysis, and its i.r. spectrum. The reaction is thought to follow S_N2 mechanism.



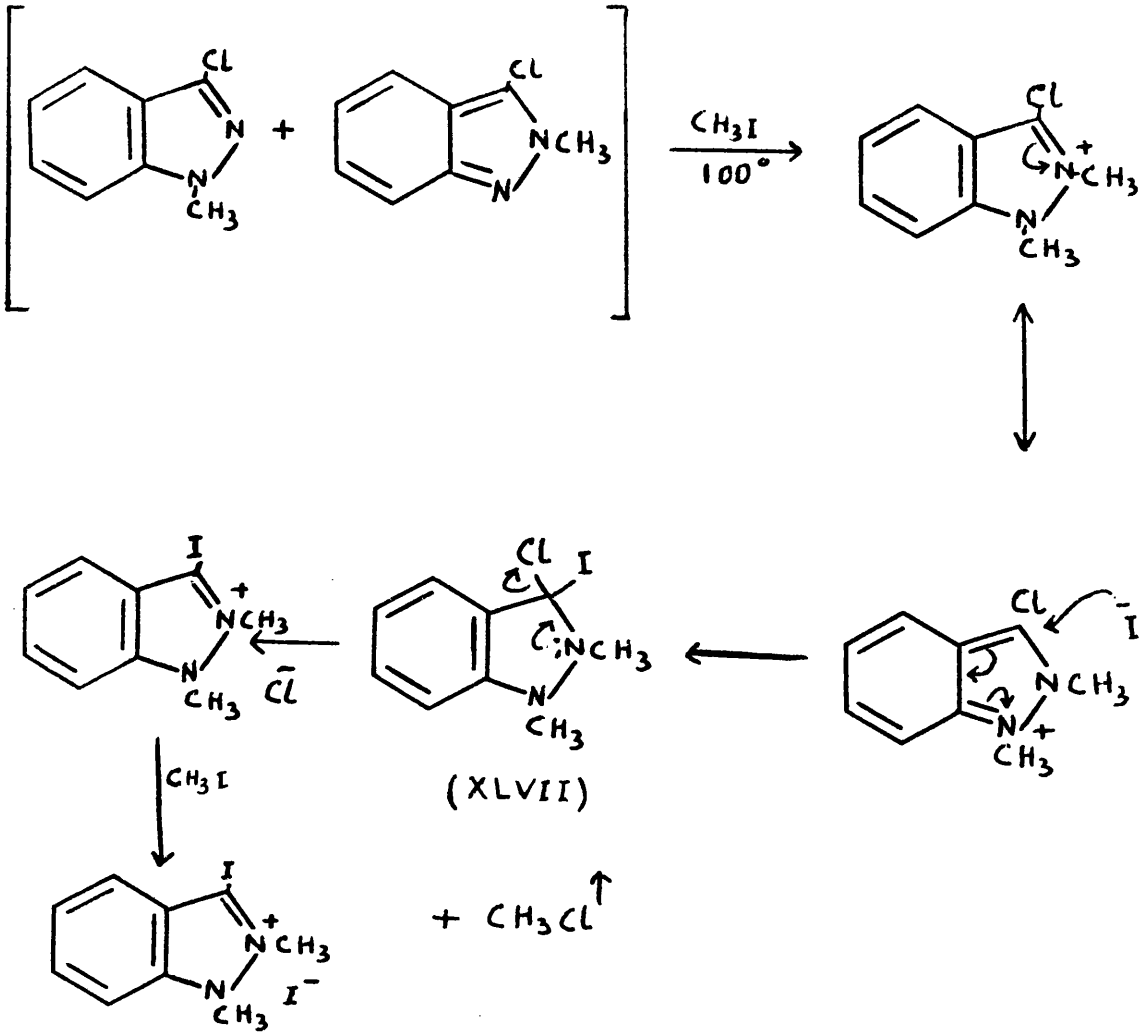
(ii) 1, 2-Dimethyl-3-iodo-indazolium Iodide.-

When the mixture of 1- and 2-methyl-3-chloroindazole was heated at 100° in a sealed tube with methyl iodide, it yielded a white solid, 1, 2-dimethyl-3-iodoindazolium iodide (XLVI)(63%). Elemental analysis did not show any chlorine and the sample was analysed for C, H, N, and I, and the results agree with the molecular formula $C_9H_{10}N_2I_2$.

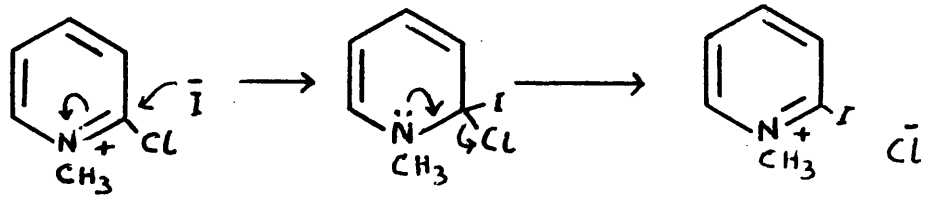


(XLVI)

It appeared that nucleophilic displacement of chlorine had occurred to give (XLVII).



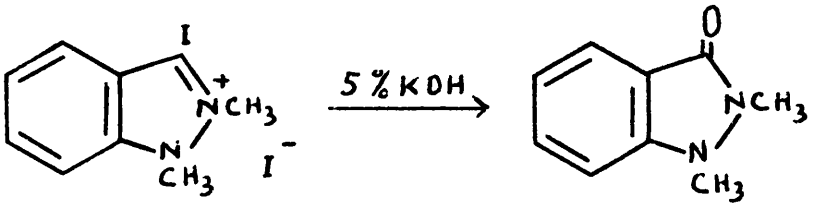
The formation of the intermediate (XLVII) is possible by analogy with N-methyl-2-chloropyridinium iodide (XLVIII).



(XLVIII)

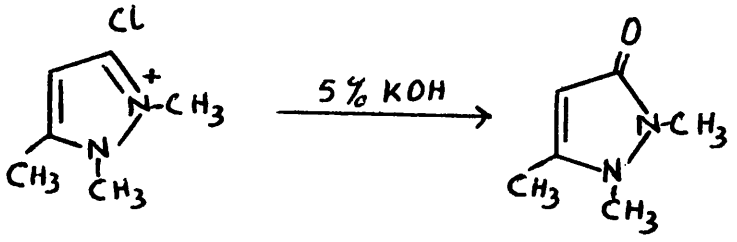
(iii) 1, 2-Dimethyl-indazolin -3-one.-

1, 2-Dimethyl-3-iodo-indazolium iodide (XLVI) reacted at room temperature with aqueous-methanolic potassium hydroxide (5%) and gave 1, 2-dimethyl-indazolin -3-one (XLIX).



(XLVI) (XLIX)

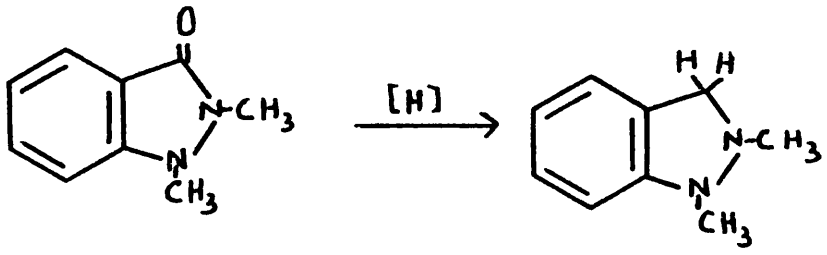
The formation of (XLIX) is analagous to the formation of 1, 2, 5-trimethyl-pyrazolin -3-one (LI). 1, 2, 5-Trimethyl-3-chloro-pyrazolium iodide (L) when treated with aqueous-methanolic potassium hydroxide (5%) has been reported[58] to yield 1, 2, 5-trimethyl-pyrazolin -3-one (LI).



(L) (LI)

(iv) 1, 2-Dimethylindazoline.-

1, 2-Dimethyl-indazolin -3-one was reduced by lithium aluminium hydride at room temperature and gave 1, 2-dimethylindazoline (XLV)(79%). The structure (XLV) was proved by elemental analysis and comparison of the b.p. with the literature[51] value. The i.r. spectrum of (XLV) did not show a (C=O) peak which was present in the spectrum of the starting material.

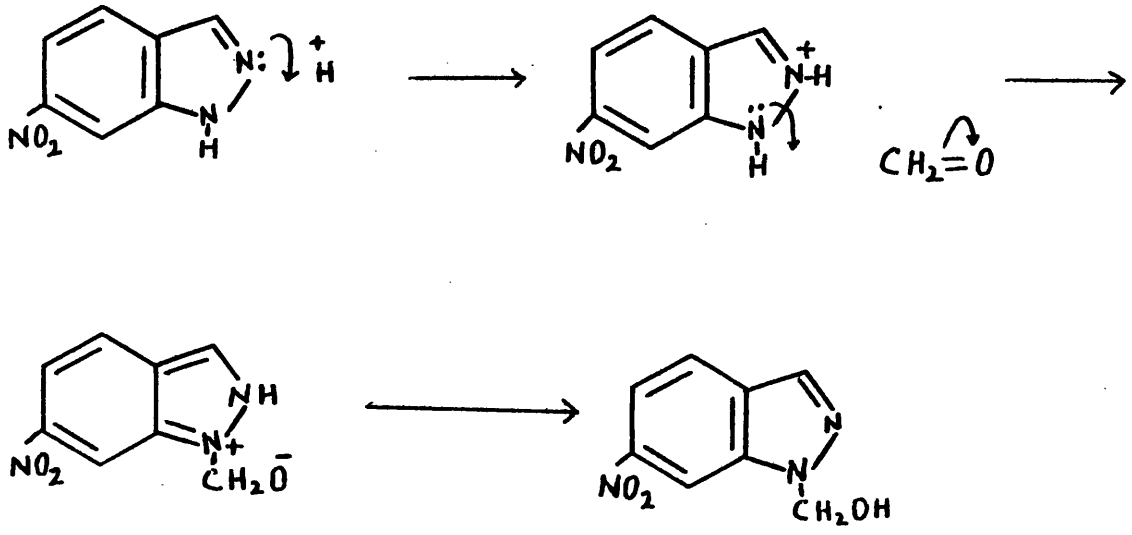


(XLIX) (XLV)

Hydroformylation of Nitroindazoles.-

(i) At room temperature

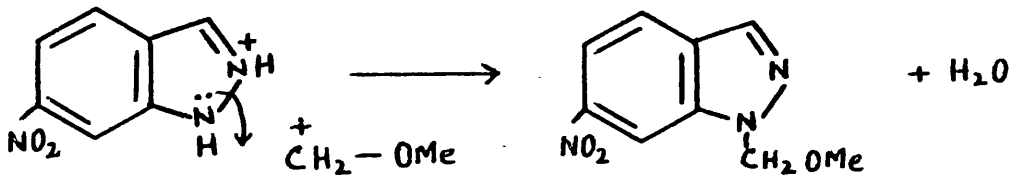
6-Nitroindazole reacted with formalin at room temperature in presence of 20% hydrochloric acid and yielded 1-hydroxymethyl-6-nitroindazole (LII), which possibly was formed by the attack of protonated 6-nitroindazolium cation on formalin.



(LII)

(ii) At 60°

The above reaction was carried out at higher temperature to see if any 2-isomer was formed. When 6-nitroindazole was heated with formalin in presence of 20% hydrochloric acid and methanol at 60°, it yielded only 1-methoxymethyl-6-nitroindazole (LIII) and no N-2 isomer was formed. The formation of 1-methoxymethyl-6-nitroindazole (LIII) might have taken place probably by acylation with a hemiacetal, formed from formalin and protonated methanol.



(LIII)

The structure (LIII) was supported by its elemental analysis, i.r. and n.m.r. spectra. The i.r. spectrum of (LIII) did not show hydroxyl absorption; the n.m.r. spectrum showed OCH_3 and CH_2 signals at 6.4 and 4.14 τ respectively.

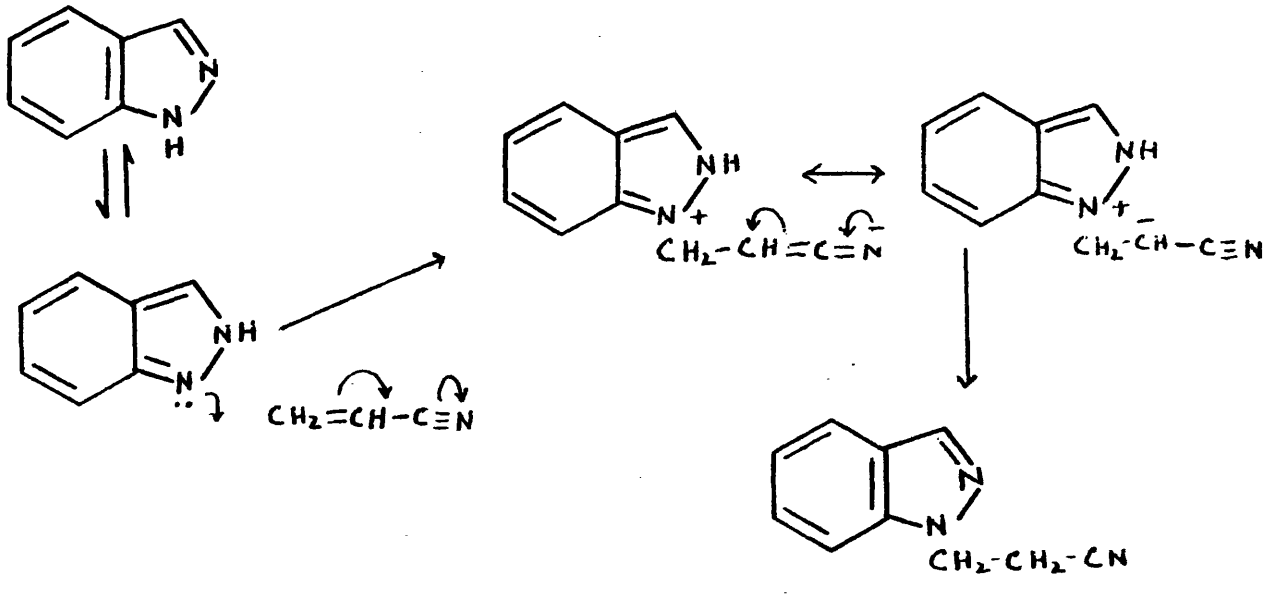
Pozharskii et al[41] have reported the formation of 1-hydroxymethylindazole and 1-hydroxymethyl-6-nitroindazole when indazole and 6-nitroindazole was treated separately with formalin at room temperature. Elguero et al[59] also have observed that indazole, 4-nitroindazole, and 5-nitroindazole on treatment with formalin at 30° yielded exclusively the 1-isomer in each case. Pozharskii et al[41] have correlated their observation by analogy with 3, 5-dimethylpyrazole which is known to give a 1-hydroxymethyl isomer.

The results of previous workers and also those obtained in the present work can perhaps be better explained on the generalization that under acidic conditions indazole and mononitroindazoles will react with formalin to give exclusively 1-isomer. It may further be added that the results of methylation of nitroindazoles with diazomethane in the presence of Lewis acid, [redacted] agree with the above generalization.

Cyanoethylation.-

Indazole.

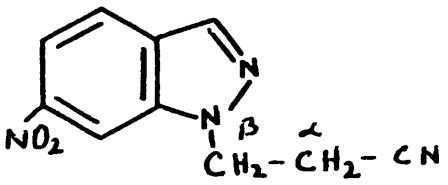
The reaction of indazole with acrylonitrile in dioxane at 70° was investigated and it was found that even at high temperature indazole reacted with acrylonitrile to give exclusively 1-isomer (LIV). The structure of 1-(2' cyanoethyl)-indazole (LIV) was confirmed by elemental analysis, i.r. and comparison of its m.p. with the reported value[6]. The formation of (LIV) could have taken place according to the scheme:



(LIV)

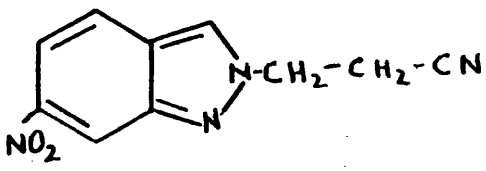
6-Nitroindazole.

6-Nitroindazole with acrylonitrile under the above conditions yielded β-(6-nitro-1-indazyl)-propionitrile (LV) and β-(6-nitro-2-indazyl)-propionitrile (LVI) in equal amounts. That the β-(6-nitro-1-indazyl) propionitrile has structure (LV) was shown by elemental analysis, i.r. and n.m.r. spectra. Its i.r. spectrum showed (-C≡N) absorption and n.m.r. showed two triplets at 6.83 and 5.08 τ which are assigned to (β-CH_2) and (α-CH_2) groups respectively. Elguero et al[59] in the n.m.r. spectrum of β-(5-nitro-1-indazyl) propionitrile have located (β-CH_2) and (α-CH_2) at 6.82 and 5.17 τ respectively.



(LV)

The elemental analysis of (LVI) gave a molecular formula $C_{10}H_8N_4O_2$ and it was thought to be the 2-isomer. Its i.r. spectrum showed (-C≡N) and (NO_2) absorptions.



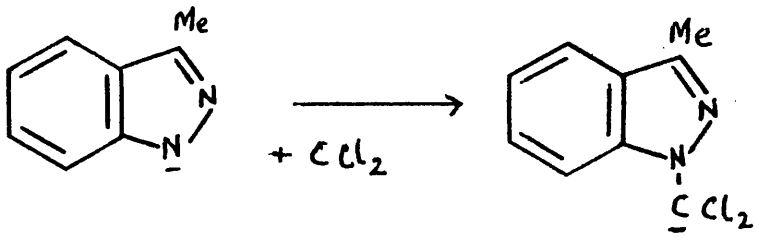
(LVI)

Indazole when reacted with acrylonitrile at 30° has been reported to yield exclusively 1-isomer.[6, 43,59] 5-Nitroindazole[59] and 6-nitroindazole[43] when reacted with acrylonitrile also give 1-isomer in each case. 7-Nitroindazole[59] under above conditions has been reported to yield 2-isomer in low yield (15%) and none of the 1-isomer. The formation of 2-isomer in the cyanoethylation reaction of 6-nitroindazole suggests that the use of a higher temperature with 4-, 5-, and 7-nitroindazole might result in the formation of both 1- and 2-isomers in each case.

Attempted Ring Expansion.-

The addition of dichlorocarbene to 3-methylindazole under neutral and basic conditions did not give any ring expanded product and unreacted 3-methylindazole was recovered in high yield. Only under basic conditions a small amount of tri (3-methyl-1-indazolyl) methane (LXI) was formed, a N-substituted product of 3-methylindazole. The formation of this tri (3-methyl-1-indazolyl) methane can be explained as follows:

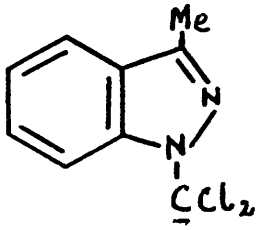
dichlorocarbene attacks the 3-methylindazolyl anion or the neutral 3-methylindazole at a nitrogen atom:



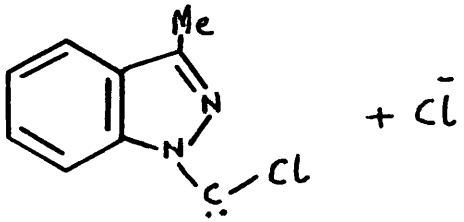
(LVII)

This new anion (LVII) can either pick up a proton to form a

1-dichloromethyl-3-methylindazole, which would be readily hydrolysed in the working up process; or heterolyse to regenerate dichlorocarbene and 3-methylindazolyl anion. However because the 3-methylindazolyl anion is not a good leaving group, the anion (LVII) dissociated in a completely different way yielding chloro (3-methyl-1-pyrazolyl) carbene (LVIII) and a chloride ion:

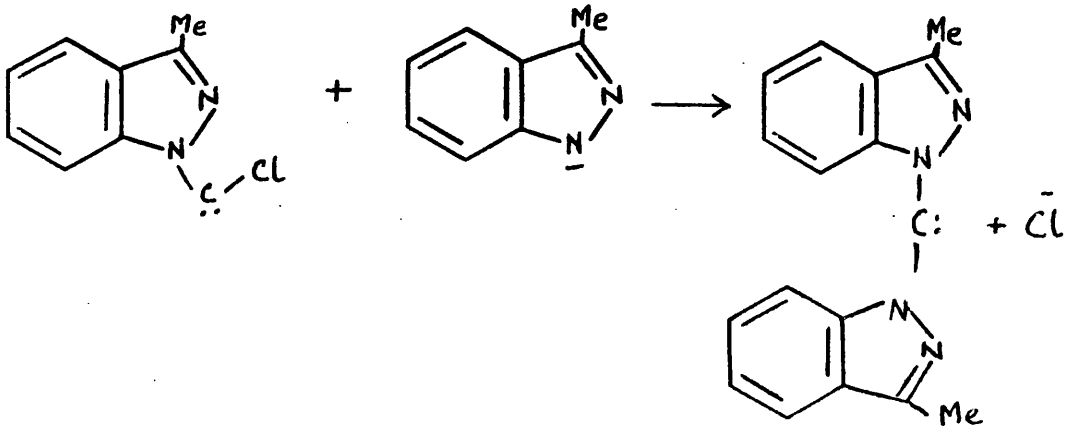


(LVII)



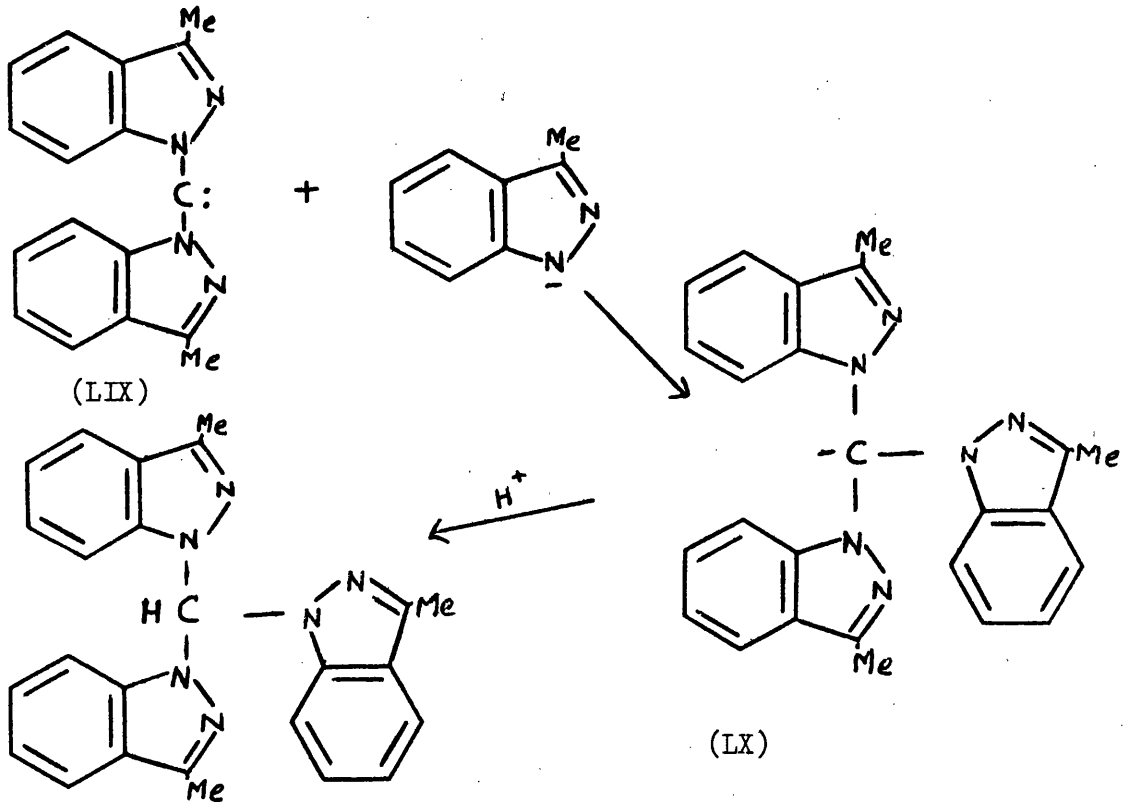
(LVIII)

This chloroindazolylcarbene (LVIII) would be fairly stable, as the orbitals of the heterocyclic ring, as well as the p orbitals of the chlorine atom, would overlap with the p orbital of the carbene atom; it could probably be considered more stable than dichlorocarbene, for example. This carbene can attack another 3-methylindazole molecule and after the loss of a second chloride ion, can form the diindazolyl carbene (LIX):



(LIX)

The π orbitals of both heterocyclic rings would fill the empty carbon orbitals of this carbene and high relative stability would be the result. Finally attack by this carbene on another 3-methyl-indazolyl anion would give the tri (3-methyl-indazolyl) methane anion (LX) which would gain a proton in the working up procedure and be isolated as tri (3-methyl-1-indazolyl) methane (LXI):



This mechanism is similar to that proposed[44] for the formation of tripyrazolylmethane by the action of dichlorocarbene on 3, 4, 5-trimethylpyrazole[44].

This tri (3-methyl-1-indazolyl) methane (LXI) was, by analogy with tripyrazolyl methane[44], extremely sensitive to acid hydrolysis and was converted to parent-3-methylindazole, and thus could not be isolated in the reaction of 3-methylindazole with sodium

trichloroacetate and 1, 2-dimethoxyethane.

Thermal Reactions of 3-phenyl-2-hydroxyindazole.-

3-Aryl-2-hydroxyindazoles have been reported[11, 61] to be rather unstable compounds which lose nitrogen when heated above their melting points and change to aryl ketones. Thus 3-phenyl-2-hydroxyindazole gives benzophenone[7], and 3-p-tolyl and 3-p-anisyl-2-hydroxyindazole are changed into p-methylbenzophenone and p-methoxybenzophenone respectively[61].

In order to establish the nature of the intermediate in the above reactions, the 3-phenyl-2-hydroxyindazole was heated above its melting point in the presence of tetraphenylcyclopentadienone in xylene. With this diene it was hoped to trap any intermediate by forming a 1:4 addition complex. The only products obtained were 3-phenylindazole and benzophenone. The same products, i.e. 3-phenylindazole and benzophenone, were obtained when 3-phenyl-2-hydroxyindazole was heated alone in xylene.

The mechanism of the formation of 3-phenylindazole is obscure. It may be regarded as the reduction product of 3-phenyl-2-hydroxyindazole. It has been reported[11, 60] that 3-aryl-2-hydroxyindazoles are reduced to 3-arylindazoles by reducing agents like zinc dust in alkali, sodium amalgum, zinc dust in acetic acid, and stannous chloride in alcohol and concentrated hydrochloric acid.

EXPERIMENTAL

GENERAL REMARKS

Solvents were dried by the usual standard methods. Methanol (analar) was dried by refluxing over magnesium and iodine, then distilled and stored over molecular sieves (type 4A).

Sodium trichloroacetate was dried before use, by heating under vacuum at 100° for 2 hr. over phosphorus pentoxide.

Chloroform (analar) was dried over anhydrous magnesium sulphate. Neutral alumina (Beckman activity 1; 240 mesh) was used for column chromatography. Chromatography columns were prepared in petroleum ether (b.p. 40-60°). Solvents were evaporated under vacuum using a rotary evaporator.

Percentage yields are based on starting materials. Melting points were recorded on a Buchi electric melting point apparatus and are uncorrected.

Infra red spectra were run in Nujol, liquid film, or KBr using a Perkin Elmer 257 spectrometer and were calibrated against polystyrene.

Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian A 60 m/c or 100 m/c spectrometer using tetramethylsilane as an internal reference.

"Petroleum" refers to petroleum ether, b.p. 40-60°.

METHYLATION OF MONO-NITROINDAZOLES.

(a) By Methyl Iodide in Dimethyl Sulphoxide.-

General method.

The nitroindazole (1g., 0.006 mole) and methyl iodide (2.82 g., 0.02 mole) in dimethyl sulphoxide (15 ml.) were stirred for 5 hr. at 70°. The reaction mixture was cooled and concentrated under reduced pressure. The residues were extracted with hot ether. The ether solutions were treated with crystals of sodium thiosulphate and dried over anhydrous sodium sulphate. After evaporation of the ether, crystallization from methanol yielded the 2-methyl isomer. In the case of 6-nitroindazole, dilution of the mother liquor with water yielded 1-methyl-6-nitroindazole. Melting points and percentage yields of the products are given in Table 6. The ether insoluble residue was boiled with methanol and charcoal. The filtrates after concentration yielded quaternary periodides, whose melting points and yields are given in Table 6.

1-methyl- and 2-methyl-5-nitroindazole

In the case of 5-nitroindazole the ether solution was evaporated and the residue dissolved in benzene was chromatographed on alumina to separate 1- and 2-methyl isomers. The elution solvents, melting points and yields are indicated in Table 6.

(b) By Methyl Toluene-p-sulphonate.-

General method.

Methyl toluene-p-sulphonate (1.1 g., 0.006 mole) was added to a solution of the mono-nitroindazole (1 g., 0.006 mole) in nitrobenzene (30 ml.). The mixture was stirred for 5 hr. at 90°. The reaction mixture was allowed to cool and then filtered. The filtrate

was chromatographed on alumina. Nitrobenzene was eluted first with petroleum. The isomers and unreacted starting materials were then separated. The solvents used for elution of isomers and starting material, melting points and yields are shown in Table 7.

(c) By Diazomethane.-

General method.

Diazomethane[47] in ether was prepared by the action of aqueous potassium hydroxide on nitrosylmethyl urea and dried over potassium hydroxide pellets for 1 hr. before use.

Diazomethane[47] (3 moles) in ether was added drop wise to a well stirred solution of nitroindazole (1 mole) in dioxane, containing boron trifluoride etherate (1 ml). The reaction mixture was stirred at room temperature for 6 hr. The white inorganic residue was filtered off, then acetic acid (1 ml) was added to the filtrate. The solvent was removed under reduced pressure and the residue taken up in methanol and chromatographed on alumina. The solvents used for elution or crystallization of isomers, melting points and yields are given in Table 8. In one experiment 6-nitroindazole was reacted with diazomethane in the absence of boron trifluoride etherate to give a mixture of 1-methyl and 2-methyl-6-nitroindazole and unreacted 6-nitroindazole. See Table 8.

Table 6

Methylation by Methyl Iodide in Dimethyl Sulphoxide.-

Indazole	methylated products (%)	elution solvent	crystallization solvent	m.p.	lit m.p. & ref.
4-Nitro	2-methyl isomer (50)	-	methanol	101°	98°, 16 101-3°, 27
	Periodide (orange)(20)	-	water	187°	-
5-Nitro	1-methyl isomer (50)	benzene:ether (1:1)	-	127°	129°, 29
	2-methyl isomer (10)	methanol	-	162°	163°, 29
	Periodide (golden)(17)	-	methanol	220°	-
6-Nitro	1-methyl isomer (10)	-	water	122°	125°, 16,31 122°, 33 108°, 45 116-8°, 46
	2-methyl isomer (50)	-	methanol	160°	160°, 31,16
	Periodide (golden)(17)	-	methanol *	170-2°	-
7-Nitro	2-methyl isomer(30)	-	ether	140°	143°, 33

* (Found: C, 19.08; H, 1.75; N, 7.29; I, 67.31. $C_9H_{10}N_3O_2I_3$ requires C, 18.86; H, 1.76; N, 7.34; I,66.2%)

Table 7

Methylation by Methyl toluene-p-sulphonate

Indazole	methylated products (%)	elution solvent	starting material recovered (%)	m.p.	lit. m.p. and ref.
4-Nitro	2-methyl isomer (60)	benzene	20	100°	98°, 16 101-3°, 27 81-82°, 5 101°, 28
5-Nitro	1-methyl isomer* (60) 2-methyl isomer** (10)	benzene:ether (1:1) methanol	30	128° 163°	129°, 29 163°, 29
6-Nitro	2-methyl isomer (50)	benzene	25	160°	160°, 16, 31 158°, 33 159°, 45, 46
7-Nitro	2-methyl isomer+ (40)	ether	50	140°	143°, 33

* $\tilde{\nu}$ max (KBr_γ) 3110, 3080, 1620, 1570, 1500, 1410, 1390 cm^{-1}
(Nujol) 3110, 3080, 1620, 1570, 1500, 1460, 1380 cm^{-1}

** $\tilde{\nu}$ max (KBr_γ) 3100, 3040, 1620, 1590, 1520, 1500, 1390 cm^{-1}
(Nujol) 3100, 3020, 1620, 1595, 1540, 1510, 1470, 1380 cm^{-1}

\+ $\tilde{\nu}$ max (Nujol) 3130, 1640, 1550, 1510, 1460, 1430, 1380 cm^{-1}

1-Me-7-nitroindazole $\tilde{\nu}$ max (Nujol) 3100, 3080, 1630, 1570, 1520, 1500, 1470, 1410, 1380 cm^{-1}

Table 8

Methylation by Diazomethane

Indazole	methylated products (%)	elution solvent	crystallization solvent	m.p.	lit. m.p. and ref.
4-Nitro	1-methyl isomer (50)	b:p (1:1)	-	140°	136°, 16, 27 139°, 28
	2-methyl isomer (50)	b	-	100°	98°, 16 101-3°, 27 81-82°, 5 101°, 28
5-Nitro	2-methyl isomer (50)	-	water	163°	163°, 29
6-Nitro	1-methyl isomer (75)	p	-	125°	125°, 16, 31
6-Nitro*	1-methyl isomer (16)	p	-	125°	125°, 16, 31
	2-methyl isomer (8)	b	-	160°	160°, 16, 31

* In the absence of boron trifluoride etherate

b benzene

p petroleum

(d) By Methyl Iodide and Sodium Methoxide.-

7-Nitroindazole (0.646 g., 0.003 mole) was added to sodium (0.12 g.) dissolved in methanol (10 ml.). Methyl iodide (1.04 g., 0.007 mole) was added and the reaction mixture stirred at 60° for 4 hr. After filtration and removal of the solvent under reduced pressure, the residue was taken up in benzene and chromatographed on alumina. The first fraction eluted with benzene/petroleum mixture (1:1) gave 1-methyl-7-nitroindazole (100 mg., 14%) m.p. 102° (lit[33]., 98°). The second band eluted with ether gave 2-methyl-7-nitroindazole (400 mg., 56 %) m.p. 142° (lit[33]., 143°).

METHYLATION OF INDAZOLE

By Methyl Iodide and Sodium Methoxide.-

Indazole (1g., 0.008 mole) was added to sodium (1.2g.) dissolved in methanol (10 ml.). The colour of the mixture immediately changed to brown. Methyl iodide (2.5g., 0.018 mole) was added and the mixture stirred at 60° for 4 hr. The oily residue left after filtration and evaporation of solvent was dissolved in methanol and chromatographed on silica gel (MFC grade). The petroleum eluate yielded unreacted indazole (500 mg., 50%). A subsequent benzene eluate gave 2-methylindazole (110 mg., 10%) m.p. 50° (lit[9]., 56°) and finally elution with benzene/ether (10:1) yielded 1-methylindazole (330 mg., 30%) m.p. 60° (lit[9]., 60-61°).

METHYLATION OF 6-HYDROXYINDAZOLE

(a) By Methyl Iodide and Sodium Methoxide.-

Sodium (0.5g.) was dissolved in methanol (30 ml.) and then

6-hydroxyindazole (2g., 0.015 mole) was dissolved in the mixture and finally methyl iodide (4.2g., 0.029 mole) was added dropwise with stirring. The reaction mixture was stirred at 60-70° for 6 hr. The solvent was removed under reduced pressure. The residue was taken up in methylene chloride and chromatographed on alumina. The first benzene eluate yielded 6-methoxyindazole (565 mg., 25%) m.p. 123-24° (Found: C, 64.30; H, 5.30; N, 19.09 $C_8H_8N_2O$ requires C, 64.92; H, 5.45; N, 18.93%). ν max (KBr) 3300 (NH), 3010, 2960, 2930, 1630 cm^{-1}. The second fraction eluted with methanol yielded a yellowish viscous oil (100 mg., 5%) which could not be purified.

(b) By Dimethyl Sulphate and Alkali.-

6-Hydroxyindazole (4g., 0.027 mole) was dissolved in aqueous potassium hydroxide (2g. in 20 ml. water). Dimethyl sulphate (3.8 g., 0.03 mole) was added to the above solution. The mixture was stirred for 3 hr. on a water bath at 40-50°. The reaction mixture was extracted with benzene and ether, and the combined extract dried over magnesium sulphate. The solvent was removed under reduced pressure to leave an oily residue which was crystallized to give 6-methoxyindazole (1.77 g., 40%) m.p. 124° (from petroleum) mixed m.p. 124°. ν max (KBr) 3300 (NH), 3010, 2960, 2930, 1630 cm^{-1}.

(c) By Diazomethane.-

(i) Without boron trifluoride etherate.

Diazomethane[48] (1.3g., 0.03 mole approx.) in ether was prepared from p-tolylsulphonylmethylnitrosoamide. 6-hydroxyindazole (4g., 0.027 mole) was added to the ethereal solution of diazomethane. The reaction mixture was stirred at room temperature overnight, and for 1 hour at 40°. The ether was evaporated under reduced pressure.

The residue was extracted with benzene. The benzene extract yielded 6-methoxyindazole (440 mg., 10%) m.p. 122-24°. The benzene insoluble residue, dissolved in hot methanol and recrystallized from boiling methanol gave 6-hydroxy-2-methylindazole (3g., 70%), m.p. 170° (lit[46]., 167-69°)(Found: C, 64.23; H, 5.49; N, 18.55. Calc for $C_8H_8N_2O$: C, 64.92; H, 5.45; N, 18.93%) ν max (KBr) 3100, 2780, 2660, 1635 cm^{-1}.

(ii) In the presence of boron trifluoride etherate.

Diazomethane[47] (2.1 g., 0.05 mole approx.) in ether was added drop wise into the solution of 6-hydroxyindazole (6.7g., 0.05 mole) in dioxane (30 ml.) containing boron trifluoride etherate (1 ml.). The reaction mixture was stirred at room temperature for 6 hr. and filtered. Acetic acid (1 ml.) was added to the filtrate and the solvent was removed under reduced pressure. The residue was extracted with benzene. The extract after removal of solvent yielded 6-methoxyindazole 0.7g., 10%) m.p. and mixed m.p. 124°, ν max (KBr)3300, 3010, 2960, 2930, 1630 cm^{-1}

The benzene insoluble residue, dissolved in hot methanol and recrystallized from boiling methanol, gave 6-hydroxy-2-methylindazole (5g., 70%) m.p. and mixed m.p. 170° (lit[46]., 167-69°) ν max (KBr) 3100, 2780, 2660, 1635 cm^{-1}.

Formation of 6-Methoxy-2-Methylindazole.-

(a) Diazomethane (0.42g., 0.001 mole approx.) in ether was added slowly to the solution of 6-methoxyindazole (0.148g., 0.001 mole) in dioxane (10 ml.) containing boron trifluoride etherate (1 drop). The reaction mixture was stirred at room temperature for 24 hr. and filtered. The solvent was removed under reduced pressure and yielded

6-methoxy-2-methylindazole as an oily residue (38 mg., 25%) which was not purified.

ν max (liquid) 3010, 2940, 1630 cm^{-1}.

(b) Diazomethane (0.42 g., 0.001 mole approx.) in ether was added drop wise into the solution of 6-hydroxy-2-methylindazole (0.148 g., 0.001 mole) in dioxane (10 ml.) containing boron trifluoride etherate (1 drop). The reaction mixture was stirred at room temperature for 24 hr. and filtered. The solvent was removed under reduced pressure and yielded 6-methoxy-2-methylindazole (38 mg., 25%)

ν max (liquid) 3000, 2960, 2940, 1630 cm^{-1}.

6-METHOXYINDAZOLE cf 49

(a) 1-(p-Nitrophenyl)-6-methoxyindazole.-

Anisaldehyde p-nitrophenylhydrazone (3.8 g., 0.01 mole) polyphosphoric acid (46 g.) and nitrobenzene (8 g.) were heated slowly with stirring during 1.5 hr. to 150°. The reaction mixture was kept at this temperature for 5 min. After cooling and dilution with water, the mixture was extracted with chloroform (3 x 100 ml.). The chloroform extracts were washed with water and dried over sodium sulphate. The solution was concentrated under reduced pressure and chromatographed on alumina. The nitrobenzene was washed off the column with petroleum. The yellow band eluted with benzene yielded 1-(p-nitrophenyl)-6-methoxyindazole (2g., 54%) m.p. 171-72° (lit.,[49] 172-73)

(b) 1-(p-Aminophenyl)-6-methoxyindazole.-

1-(p-Nitrophenyl)-6-methoxyindazole (2.7 g., 0.01 mole) was dissolved in acetic acid (36 ml.), then hydrochloric acid (36 ml.) and stannous chloride (15 g.) were added. The mixture was heated for

20 min. cooled and diluted with water. The solution was made alkaline with potassium carbonate and extracted with ether. The ether extracts were washed with water and dried over sodium sulphate. After removing the ether the residue was crystallized from alcohol - ether and yielded 1-(p-aminophenyl)-6-methoxyindazole (1.3 g., 56.6%) m.p. 100° (from ether) (Found: C, 70.99; H, 5.41; N, 16.83. $C_{14}H_{13}N_3O$ requires C, 70.35; H, 5.48; N, 17.58%)

ν max (KBr) 3420, 3340 (NH_2) 3230, 3000, 1625 cm^{-1}.

(c) 6-Methoxyindazole.-

1-(p-Aminophenyl)-6-methoxyindazole (1g., 0.004 mole) was dissolved in 25% sulphuric acid (18 ml.). Sodium dichromate (0.454 g.) in water (50 ml.) was added to the acidic solution. After 2 hr. at 0° the mixture was diluted with water and steam distilled to remove p-benzoquinone. The mother liquor was made alkaline with sodium hydroxide solution and extracted with ether. The ether extract washed with water and dried over sodium sulphate. Ether-benzene crystallization gave 6-methoxyindazole (100 mg., 16.6%) m.p. and mixed m.p. 124°.

SYNTHESIS OF 1, 2-DIMETHYLINDAZOLINE

(a) 1- and 2-Methyl-3-chlorindazole.-

3-Chloroindazole (10 g., 0.06 mole) was dissolved in concentrated methanolic potash solution (20 ml.). Methyl iodide (26 g., 0.18 mole) was added. The reaction mixture was refluxed at 50° for 7 hr. and then stirred at room temperature overnight. The white inorganic residue was filtered off. The filtrate was concentrated under reduced pressure. The residue was treated with water and extracted with benzene. The benzene extract after the evaporation of solvent under reduced pressure yielded a mixture of 1- and 2-methyl-3-chloroindazole

(6.54 g., 60%) yellowish oil b.p. 68°/3 mm (lit.[10], 128-29/10 mm.), which was 1-methyl-3-chloroindazole and 120-21°/10 mm, 2-methyl-3-chloroindazole)

ν max (liquid) 3060, 2980, 2940, 2860, 1620 cm^{-1}

(b) 1, 2-Dimethyl-3-iodo-indazolium iodide.-

The mixture of 1-and 2-methyl-3-chloroindazole (3.3 g., 0.018 mole) and methyl iodide (7.5 g., 0.05 mole) was heated in a sealed tube at 100° for 7 hr. The brownish residue was boiled with methanol and charcoal and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue crystallized from methanol giving a white solid, 1, 2-dimethyl-3-iodo-indazolium iodide m.p. 220° (lit.[50], 220°).

(c) 1, 2-Dimethyl-3-indazolin—3 one.-

Potassium hydroxide (2.5 g., 0.04 mole) was dissolved in water (25 ml.) and methanol (25ml.). In this solution was suspended 1, 2-dimethyl-3-iodo-indazolium iodide (4.22 g., 0.01 mole). The reaction mixture was stirred for 0.5 hr. at room temperature until a clear solution was obtained. The stirring was continued for 4 hr. then the solvent was evaporated under reduced pressure. The residue was treated with water and extracted with ether. The ether extract was concentrated to give 1, 2-dimethyl-3-indazolin—3-one (1.368 g., 90%) m.p. 60° (from petroleum) (lit.[38], 66°)

ν max (KBr) 2970, 2930, 2880, 1670, 1620 cm^{-1}.

(d) 1, 2-Dimethylindazoline.-

Lithium aluminium hydride (4 g., 0.05 mole) was suspended in ether (50 ml.) and 1, 2-dimethyl-3-indazolin—3-one (7 g., 0.0 3 mole) in ether (100 ml.) was added slowly; immediately a vigorous reaction took place. After the addition of 1, 2-dimethyl-3-indazolin—3-one

was complete (10 min .), the reaction mixture was stirred at room temperature overnight. The complex was decomposed by water and extracted with ether. The ether extract was dried over sodium sulphate. The ether was removed under reduced pressure leaving behind 1, 2-dimethylindazoline (5 g., 79.3%) as colourless oil b.p. 48-50°/3 mm (lit[51]., 90-92°/12 mm) (Found: C, 72.26; H, 8.42; N, 19.66. Calc. for $C_9H_{12}N_2$: C, 73.03; H, 8.17; N, 18.93%)

ν max (liquid) 3050, 3030, 2960, 2860, 2780, 1610 cm^{-1}.

HYDROFORMYLATION OF 6-NITROINDAZOLE

(i) At Room Temperature.-

6-Nitroindazole (1.63 g., 0.01 mole) was dissolved in methanol (40 ml.) and 20% hydrochloric acid (20 ml.). Aqueous formalin (40%; 5ml.) was added to the methanolic solution of 6-nitroindazole. The reaction mixture was stirred at room temperature for 2 hr. The yellow precipitate was filtered off and crystallized from methanol to yield 1-hydroxymethyl-6-nitroindazole (1 g., 51.7%) m.p. 150° (lit[41]., 150°).

ν max (KBr) 3300 (broad), 3100, 1595, 1520 cm^{-1}

n.m.r. (d6DMSO)τ 4.12 (3H, OH, CH_2), 2.00 (2H)

1.68 (1H), 1.25 (1H).

(ii) At 60°.-

6-Nitroindazole (1.63 g., 0.01 mole) was dissolved in methanol (40 ml.) and 20% hydrochloric acid (20 ml.). Aqueous formalin (40%; 5 ml) was added to the methanolic solution. After 10 min. a yellow precipitate started to appear, which then disappeared on refluxing at 60° for 4 hours. After the reaction was completed, the solvent was removed under reduced pressure. Crystallization of the yellow residue

with methanol gave 1-methoxymethyl-6-nitroindazole (1.2 g., 58%) m.p. 124° (Found: C, 52.20; H, 4.49; N, 20.44. $C_9H_9N_3O_3$ requires: C, 52.22; H, 4.38; N, 20.3%).

ν max (KBr) 3105, 3070, 2940, 2840, 1595, 1530 cm^{-1}.

n.m.r. ($CDCl_3$) τ 6.64 (3H, $O.CH_3$) 4.14 (2H, $N-CH_2$) 2.01 (1H, aromatic) 1.50 (1H, aromatic) 1.81 (2H).

CYANOETHYLATION

Indazole.-

Indazole (1g., 0.008 mole) was dissolved in dioxane (10 ml.). Acrylonitrile (0.44 g., 0.008 mole) and benzyltrimethyl-ammonium hydroxide (40% in methanol, 0.5 ml.) was added to the indazole solution. The light yellow reaction mixture was stirred at room temperature for 2 hr. and then heated at 70° for 5 hr. The solvent was removed under reduced pressure. The orange oily residue was then dissolved in methanol and chromatographed on alumina. The ether eluate gave 1-(2'-cyanoethyl)-indazole (0.9 g., 62.5%) m.p. 84° (lit.[6], 82-84°) (Found: C, 70.12; H, 5.20; N, 24.62. Calc for $C_{10}H_9N_3$: C, 70.23; H, 5.31; N, 24.58%).

ν max (KBr) 3130, 3000, 2260 ($C\equiv N$), 1620 cm^{-1}.

The mother liquor left after the crystallization contained another white solid (c.a. 5%) m.p. 65-59°, probably 2-(2'cyanoethyl)-indazole, which however could not be isolated in pure form.

6-Nitroindazole.-

To 6-nitroindazole (5 g., 0.03 mole) in dioxane (50ml.) was added acrylonitrile (1.6 g., 0.03 mole) and benzyltrimethylammonium hydroxide (40% in methanol, 1.5 ml.). The reaction mixture was

refluxed with stirring for 4 hr. at 60-70° and then stirred for a further 2 hr. at room temperature. The reaction mixture was concentrated under reduced pressure to an oily residue. The extraction with ether, benzene and methanol of the oily residue yielded β-(6-nitro-1-indazyl)-propionitrile (2 g., 30%) m.p. 192° (lit[43], 192°). (Found: C, 55.47; H, 3.68; N, 27.09. Calc. for $C_{10}H_8N_4O_2$: C, 55.60; H, 3.73; N, 25.94 %).

ν max (KBr) 3120, 3080, 2980, 2940, 2260 (-C≡N), 1525 cm^{-1} (NO_2)

n.m.r. (d6DMSO) τ 6.82 (t, 2H, CH_2) (7 cps.) 5.08 (t, 2H, CH_2) (7 cps.) 1.98 (2H, aromatic) 1.56 (1H, aromatic) 1.20 (1H, aromatic).

The residue left after the extraction with ether, benzene and methanol was boiled with water and filtered. The yellow filtrate after concentration yielded β-(6-nitro-2-indazyl)-propionitrile (2 g., 30%) m.p. 125-26° (Found: C, 55.42; H, 3.74; N, 27.04. $C_{10}H_8N_4O_2$ requires C, 55.60; H, 3.73; N, 25.94%).

ν max (KBr) 3140, 3080, 2940, 2860, 2260 (-C≡N), 1525 cm^{-1} (NO_2).

Reaction of 3-methylindazole with Dichlorocarbene.-

(a) Under basic conditions.

3-Methylindazole (13.2 g., 0.1 mole) was added to a solution of sodium (6 g., 0.25 mole) in absolute ethanol (110ml.) and the mixture was treated with chloroform (25 ml.) in ethanol (25 ml.) at 55° for 18 hr. under nitrogen. The solution was then filtered free from sodium chloride and evaporated to dryness. The brownish-white residue was taken up in dilute alkali and thoroughly extracted with ether. The aqueous layer was then neutralised to pH = 7, and again thoroughly extracted with ether. The extracts were combined. The

solvent was removed under reduced pressure. The residual brown solid showed two spots and a long streak by t.l.c. One of the spots corresponded to starting material, 3-methylindazole. The above brown residue was chromatographed over alumina. The first fraction eluted with a mixture of petroleum/ether (1:1) yielded tri(3-methylindazol-1-yl)methane (1.0 g., 2.4%) m.p. 195° from petroleum.

(Found: C, 73.73; H, 5.54; N, 20.79. $C_{25}H_{22}N_6$ requires C, 73.95; H, 5.46; N, 20.70%).

ν max (KBr) 3060, 2930, 1620, 1450-1435 cm^{-1}.

n.m.r. ($CDCl_3$) τ 7.52 (9H, 3 CH_3 groups), 2.51 (3 H, aromatic), 2.90 (9H, aromatic), 1.02 (1H, $\geq$C-H).

Mass spectrum showed a parent peak at m/e 406 (weak), ($C_{25}H_{22}N_6$ = 406). The strong peak at m/e 275 due to loss of one unit of 3-methylindazle anion ($C_8H_7N_2$). The unit 275 in mass spectrum gives several small mass loss peaks. The peak at m/e 234 associated with the expulsion of small stable moiety CH_3CN. The peak at 143 is due to allylic cleavage of mass unit 275. The second eluate with ether gave unreacted 3-methylindazole (6.6 g., 50%) confirmed by infra-red spectrum and melting point comparison with authentic sample of 3-methylindazole.

(b) Under neutral conditions.

3-Methylindazole (21.6 g., 0.165 mole) and sodium trichloroacetate (90 g., 0.49 mole) were heated in refluxing 1, 2-dimethoxyethane (210 ml) for 24 hr. under nitrogen. The colour of the reaction mixture changed to dark brown. The solution was filtered and solvent removed under reduced pressure to give a dark brown residue, insoluble in dilute hydrochloric acid. It was taken

up in dichloromethane and chromatographed over aluminium oxide in petroleum. Prolonged elution of the column with petroleum did not give any product. Finally ether elution yielded unreacted 3-methylindazole (20 g., 92.6%). This was checked by mixed m.p. and i.r. of an authentic sample.

Thermal Reaction of 2-Hydroxy-3-phenylindazole.-

2-Hydroxy-3-phenylindazole (1.05 g., 0.005 mole) was added to a solution of tetraphenylcyclopentadienone (0.96 g., 0.0025 mole) in xylene (15 ml.) and stirred at 125-30° for 3 hr. Additional 2-hydroxy-3-phenylindazole in three portions (0.5, 1.1g. and 0.4 g.) was added to the reaction mixture at 20 min. intervals and heated for a further hr. at the same temperature. The mixture was allowed to cool and chromatographed over alumina. The xylene was eluted first with petroleum . Finally elution with ether gave a yellow oil. The infra red spectrum of this oil indicated the presence of benzophenone, tetraphenylcyclopentadienone and 3-phenyindazole.

ν max. yellow oil (liquid) 3200-3300 (broad), 1720, 1660, 1625, 1615, 1605 cm^{-1}., t.l.c. showed two spots and a long streak. These two spots in t.l.c. correspond to benzophenone and 3-phenylindazole.

The oil was treated with petroleum which precipitated 3-phenylindazole (0.281 g., 10%) as a dirty yellow solid m.p. 95°. Further repeated crystallisation from ether/petroleum raised the melting point to 110-12°. Lit[7-9]., 107-108° and 115-116° (Found: C, 81.19; H, 5.32; N, 13.37, Calc. for $C_{13}H_{10}N_2$ C, 80.48; H, 5.20; N, 14.44%).

ν max (Nujol) 3150 (=N-H stretching) and 1630 cm^{-1}

This spectrum was identical with an authentic sample of 3-phenylindazole. Mass spectrum showed a parent peak at m/e 194, ($C_{13}H_{10}N_2$ = 194)

N-Methyl-5-nitro-benzimidazole

Diazomethane (1 mole) was added drop wise to the stirred solution of 5-nitrobenzimidazole (1 mole) in dioxane containing boron trifluoride etherate (1 ml.). The reaction mixture was stirred for 6 hr. at room temperature and filtered. Glacial acetic acid (1 ml.) was added to the filtrate, and the solvent removed under reduced pressure. The residue was extracted with benzene. The benzene extract after crystallization yielded N-methyl-5-nitrobenzimidazole (20%) m.p. 150° (from benzene). (Found C, 54.47; H, 3.93; N, 24.00 $C_8H_7N_3O_2$ requires C, 54.28; H, 3.99; N, 23.74%)

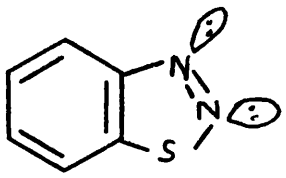
ν max (KBr) 3100, 1620, 1595, 1520, 1470 cm^{-1}.

SECTION II

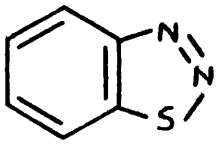
INTRODUCTION

BENZOTHIADIAZOLE

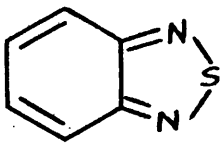
Benzothiadiazole may be regarded as the member of the benzodiazole family, in which a methine group has been replaced by a sulphur atom, but the two nitrogen atoms are of the pyridine type, each retaining a non bonded pair of electrons.



There are two possible benzothiadiazoles, 1, 2, 3-benzothiadiazole (I) and 2, 1, 3-benzothiadiazole (II). Both have been known for about eighty six years and the chemistry of both of these compounds has been thoroughly studied.



(I)



(II)

Molecular orbital considerations of (I) reveal that this is also a ten π electron system, in which each of the six carbon atoms of the carbocyclic ring contributes one pz electron, whilst the sulphur atom donates two p electrons and each of the two nitrogen atoms one p electron.

NOMENCLATURE

1, 2, 3-Benzothiadiazole (I) has been reported under a variety of names including: Phenyldiazosulphide, o-phenylenediazosulphide, isopiazthiol, benzothiodiazole, benzthiadiazole, benzothiadiazole, benz-1, 2, 3-thiodiazole, and benzo-1, 2, 3-thiadiazole.

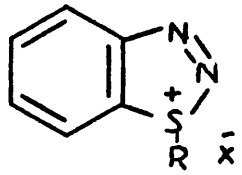
QUATERNIZATION REACTIONS

Jacobson and his co-workers in a series of papers[61-64] prepared several methyl-1, 2, 3-benzothiadiazoles, and showed the great stability of the hetero ring to a number of reagents.

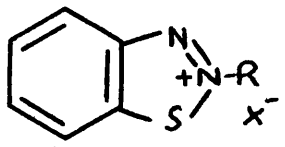
Hantzsch[65] confirmed the difficulty of quaternising 1, 2, 3-benzothiadiazole and observed that the methiodide showed a number of colour changes in different solvents. Jacobson and Janssen[61] obtained methyl and ethyl-1, 2, 3-benzothiadiazolium iodides as red crystals by heating the base with a ten-fold excess of the respective alkyl iodide in a sealed tube at 100° for one to three days.

Nunn, Chadbourne and Ralph[66] have shown that 1, 2, 3-benzothiadiazole combines with one molecular proportion of alkylating agent. They employed dialkyl sulphates, alkyl toluene-p-sulphonate and alkyl 2, 4-dinitrobenzene sulphonates for the quaternisation of 1, 2, 3-benzothiadiazole.

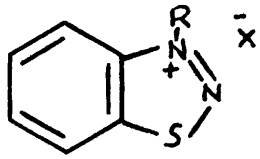
Several authors have speculated about the position of alkylation on the quaternary salts of 1, 2, 3-benzothiadiazole. Hantzsch[65] and Jacobson[61] suggested that alkylation occurred on the sulphur atom (III).



(III)



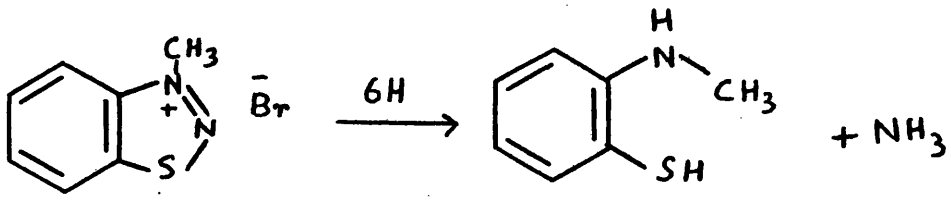
(IV)



(V)

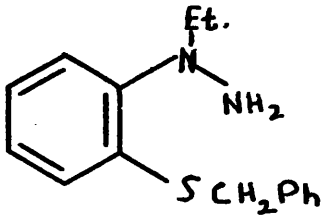
where (R = Me, Et.)

Bambas in his review article[67] mentions three possibilities (III), (IV) and (V). In review articles by Hodgson and Dodgson[68] and Sherman[69] the colour changes in the salts are attributed to structures which might result from a sulphonium salt, and thus support the idea of alkylation on the sulphur atom. Nunn et al[66] found that reduction of methyl-1, 2, 3-benzothiadiazolium bromide with tin and concentrated hydrochloric acid led to the formation of 2-methylaminothiophenol and ammonia according to the following reaction:



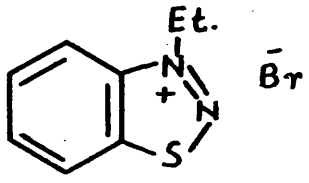
They suggested the possibility of quaternisation on N-3, but did not consider this conclusive since re-arrangement could have taken place. None of these authors definitely established the position of alkylation in the quaternary salts of 1, 2, 3-benzothiadiazole.

In this thesis a direct synthesis of 3-ethyl-1, 2, 3-benzothiadiazolium bromide (VII) from 2-aminophenylbenzyl sulphide (X) is described. 2-Aminophenylbenzyl sulphide was converted to the hydrazine (VI) by acylation, reduction, nitrosylation and finally reduction with lithium aluminium hydride.



(VI)

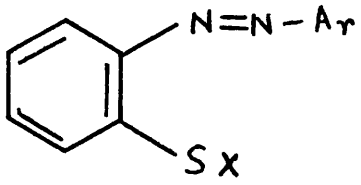
N-Ethyl-2-hydrazinophenylbenzyl sulphide (VI) heated in glacial acetic acid with hydrobromic acid and bromine, ring closed to give 3-ethyl-1, 2, 3-benzothiadiazolium bromide (VII), identical with the compound obtained by quaternisation.



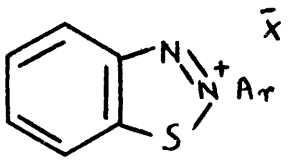
(VII)

Burawoy and his co-workers[72, 75] in a series of papers on o-mercapto-azo-compounds reported on the preparation and properties of azobenzene-2-sulphenyl derivatives (VIII). A detailed analysis of the electronic spectra of the azobenzene-2-sulphenyl halides,

thiocyanates and perchlorates showed they existed in water as true salts, involving the 2-phenyl-1, 2, 3-benzothiadiazolium cation (IX).



(VIII)

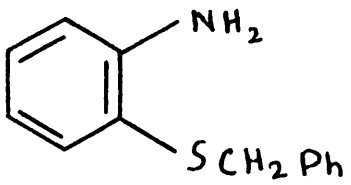


(IX)

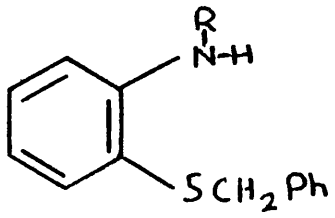
Azobenzene-2-sulphenyl bromide (i.e. 2-phenyl-1, 2, 3-benzothiadiazolium bromide) was obtained by several methods. Debenzylation of 2-benzylthioazobenzene (VIII where X = CH_2Ph) with hot concentrated hydrobromic acid alone or mixed with acetic acid, yielded instead of o-mercaptoazobenzene, 2-phenyl-1, 2, 3-benzothiadiazolium bromide (ca 50%). Heating 2-benzylthioazobenzene with 1 mole of bromine in acetic acid yielded, almost quantitatively, benzyl bromide and the corresponding sulphenyl bromide (i.e. quaternary salt).

DISCUSSION OF RESULTS

In order to decide the position of alkylation in the quaternary salts of benzothiadiazole, the initial step was to synthesise N-alkyl-2-aminophenylbenzyl sulphide (XI)(where R = Me, Et.) from 2-aminophenylbenzyl sulphide (X).

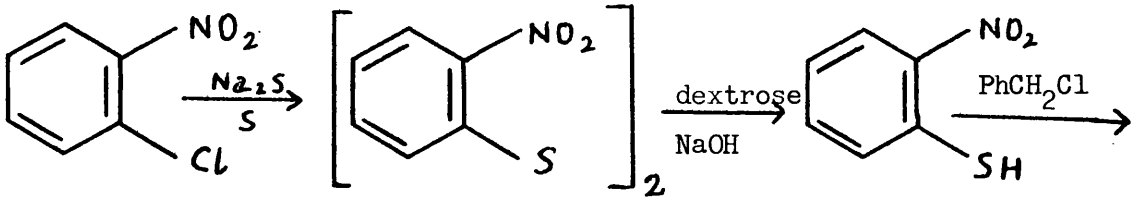


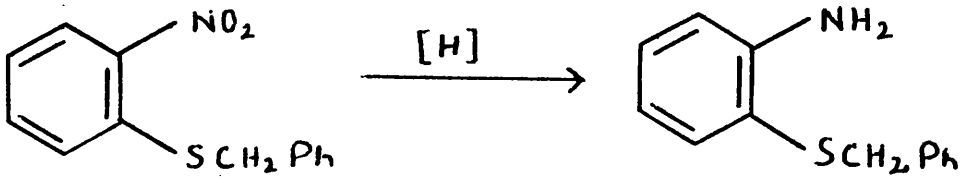
(X)



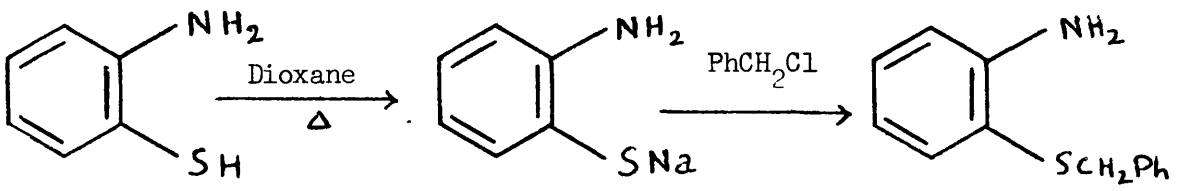
(XI)

2-Aminophenylbenzyl sulphide (X) had been made previously in poor yield by a lengthy process,[70-74]





consequently a more convenient route was sought. This was achieved by the direct benzylation of the sodium salt of 2-aminothiophenol according to the following sequence:

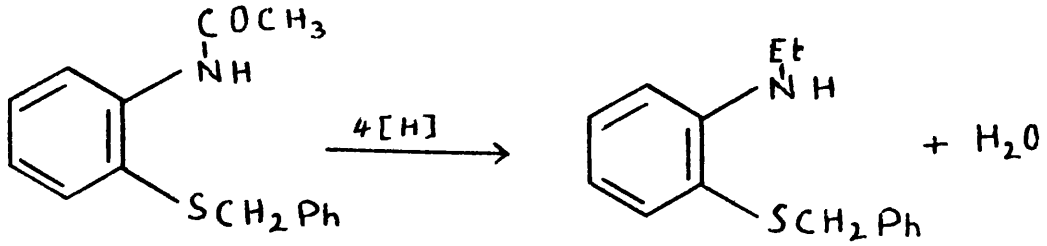


Direct benzylation of 2-aminothiophenol itself would result in the benzylation of both the thiol and amino groups. However the thiol group being acidic reacts readily with sodium metal to give a sodium salt with the evolution of hydrogen gas. The addition of benzyl chloride to a suspension of the sodium salt resulted in formation of 2-aminophenylbenzyl sulphide (X) in high yield.

N-Alkylation of 2-Aminophenylbenzyl Sulphide (X).-

N-Methyl-2-aminophenylbenzyl sulphide (XI where R = Me.) was synthesised by mono methylation of the primary amine (X) with dimethyl sulphate/alkali and also by heating it with excess methyl iodide. However the yield of desired product was very low (9.3 and 5% respectively) and these methods were not studied further. The possibility of the formation of tertiary and quaternary compounds in these reactions cannot be ruled out, although the separation of these by column chromatography was unsuccessful.

N-Ethylation of compound (X) was achieved by heating it with triethyl orthoformate in the presence of concentrated sulphuric acid, giving N-ethyl-2-aminophenylbenzyl sulphide (XIII)(28.5%) as an oil. This compound was prepared in high yield (98.1%) by the reduction of N-acetyl-2-aminophenylbenzyl sulphide (XII) with lithium aluminium hydride.



(XII) (XIII)

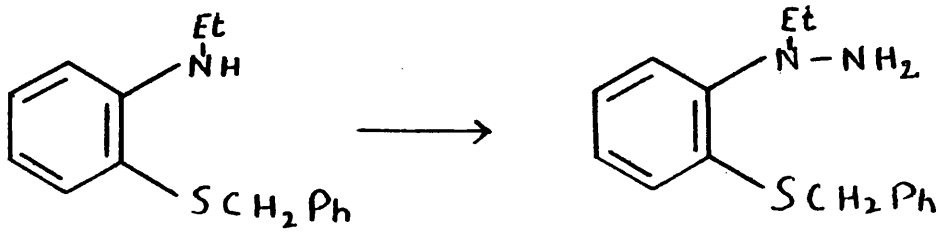
The results are summarised in Table 1.

Table 1

N-Alkylation of 2-Aminophenylbenzyl Sulphide (X).-

Reactants ratio	Time/Temp.	(%) yield	R in (XI)
(X) + Dimethyl sulphate 1 : 1.5	2 hr/80°	18.7	Me.
(X) + Methyl iodide 1 : 3	3 hr/60°	5	Me.
(X) + Triethyl-orthoformate 1 : 1.5	3 hr/180°	28.4	Et.
(XII) + Lithium aluminium hydride 1 : 2	4 hr/room temperature	96.4	Et.

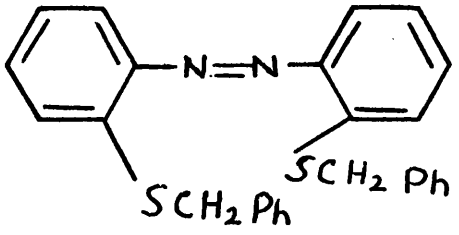
N-Amination of N-Ethyl-2-Aminophenylbenzyl Sulphide (XIII).-



(XIII) (VI)

The N-amination of N-ethyl-2-aminophenylbenzyl sulphide (XIII) with monochloramine in the presence of strong base sodium hydride and also with alkaline hydroxylamine-O-sulphonic acid was not very successful, and resulted in the formation of dark gummy residues from which the pure N-ethyl-2-hydrazinophenylbenzyl sulphide (VI) could not be isolated even by column chromatographic techniques. However the presence of (VI) in the reaction products was suspected after comparing the i.r. spectrum of the above gummy residues with i.r. spectra of (XIII) and phenylhydrazine (see Table 2).

In an attempt to N-aminate the 2-aminophenylbenzyl sulphide (X) with monochloramine in the presence of sodium hydride, a small amount of an orange compound, 2, 2' dibenzylthioazobenzene[76] (XV) was isolated, together with unreacted starting material (X)(60%).

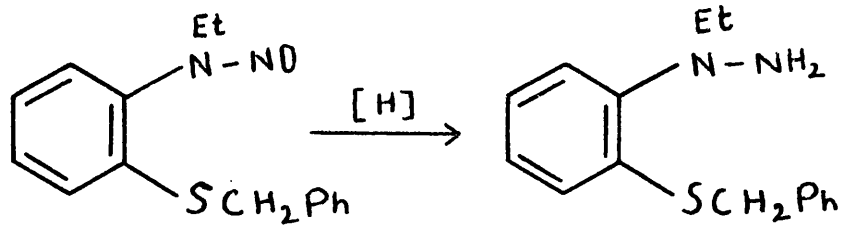


(XV)

The compound (XV) m.p. 170^{d} analysed for $C_{26}H_{22}N_2S_2$ and is thought to be the cis-isomer because the m.p. of it differed considerably from that reported by Burawoy et al[76]. These workers prepared this compound by the reduction of 2-benzylthionitrobenzene with lithium aluminium hydride.

It appeared that monochloramine was behaving as an oxidising agent rather than aminating agent (see Section III).

Alternatively N-amination might be achieved by nitrosylation of (XIII) to form N-ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV) and then reduction.



(XIV) (VI)

Synthesis of N-Ethyl-N-nitroso-2-aminophenylbenzyl Sulphide (XIV).-

The nucleophilic substitution at nitrogen of N-ethyl-2-aminophenylbenzyl sulphide (XIII) by nitrosyl cation ($\overset{+}{N}$=O) would result in the formation of N-ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV). It was found that nitrosyl bromide was practically unreactive, whereas nitrous acid was a good nitrosylating agent.

When (XIII) was treated with nitrosyl bromide in ether it resulted in a dark black gummy residue, which could not be purified. However N-ethyl-2-aminophenylbenzyl sulphide (XIII) reacted with nitrous acid at moderate temperature and gave N-ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV)(55.5%). The structure of (XIV) was confirmed by analysis, i.r. and n.m.r. spectra.

Reduction of (XIV) to N-Ethyl-2-hydrazinophenylbenzyl Sulphide (VI). -

(a) By sodium dithionite ($Na_2S_2O_4$) .

Overberger et al[74] have reduced dialkyl-N-nitrosoamines to hydrazines with alkaline sodium dithionite. Applying the same idea, compound (XIV) was reduced by sodium dithionite in alkaline medium and yielded (VI)(10%) as a dark viscous oil which could not be purified, but i.r. spectrum of this product was identical with i.r. spectra of (VI) obtained by different reactions (See Table 2).

(b) By hydrogen in the presence of Palladium on charcoal and Adam's catalyst mixture.

When the compound (XIV) was reacted for 3 days with hydrogen in the presence of a mixed catalyst (Palladium on charcoal and Adam's catalyst) in acetic acid and ethanol, only a quarter of the calculated amount of hydrogen was absorbed and the product (VI) obtained in low yield (c.a. 10%) as a dark gummy residue. The infra red spectrum was identical with that of an authentic sample (See Table 2).

(c) By lithium aluminium hydride.

N-Ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV) was reduced to N-ethyl-2-hydrazinophenylbenzyl sulphide (VI) almost quantitatively by lithium aluminium hydride at 60° for 6 hr. This method of reduction is superior to the above reduction methods.

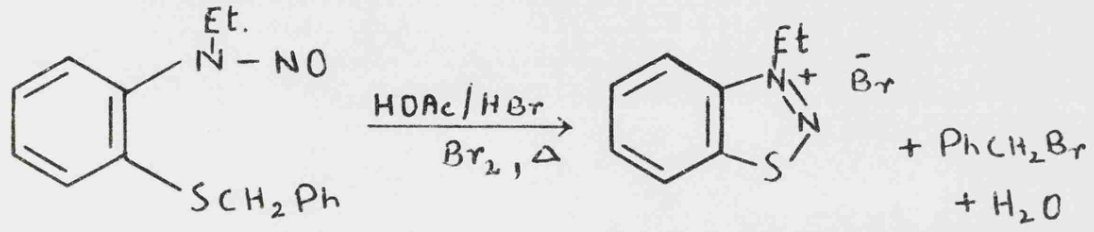
Table 2. - Comparison of i.r. spectra

Source of compound	Solvent	(N-H) region $cm.^{-1}$	(C-H) region $cm.^{-1}$	(CH_3, CH_2) region $cm.^{-1}$	aromatic (C=C) region $cm.^{-1}$
N-Ethyl-2-aminophenylbenzyl sulphide (XIII)	liquid film	3375 (singlet) (strong)	3060, 3030 (medium)	2970, 2930 (medium)	1590
Phenylhydrazine	liquid film	3360-3300 (broad and weak)	3060, 3030 (weak)	-	1610
(XIII) + Monochloramine	liquid film	3360-3300 (broad and weak)	3060, 3030 (weak)	2970, 2930 (medium)	1600
(XIII) + HOSA	liquid film	3370	3060, 3030 (medium)	2970, 2930 (medium)	1595
N-Ethyl-N-Nitroso-2-amino-phenylbenzyl sulphide (XIV)	KBr	-	3060, 3030 (medium)	2980, 2940, 2930 (medium)	1590*
(XIV) + Lithium aluminium hydride	liquid film	3400-3320 (broad) weak	3060, 3020 (medium)	2970-2930 (medium)	1590
(XIV) + $Na_2S_2O_4$	liquid film	3360-3320 (broad) weak	3060, 3030 (medium)	2970, 2830 (medium)	1590
(XIV) + Pd/C and Adam catalyst	liquid film	3380-3340	3060, 3020 (medium)	2960, 2920 (medium)	1590

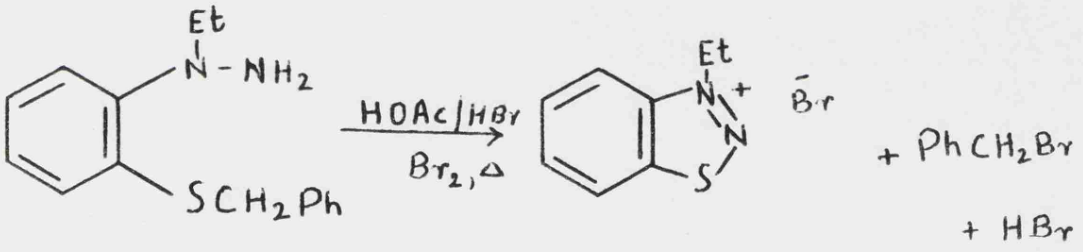
HOSA = Hydroxylamine-o-sulphonic acid

* = 1445, 1428 $cm.^{-1}$ (strong doublet) (N=O stretchings)

It was considered that either of the compounds (XIV) or (VI) might be ring closed and debenzylated by heating with acetic acid and hydrobromic acid i.e. by Burawoy's method[75], to give 3-ethyl 1, 2, 3-benzothiadiazolium bromide (VII) according to the following scheme:



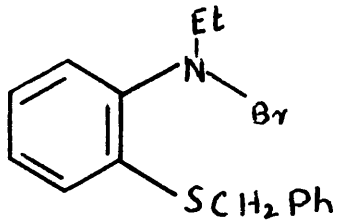
(XIV) (VII)



(VI) (VII)

Attempted ring Closure of (XIV).-

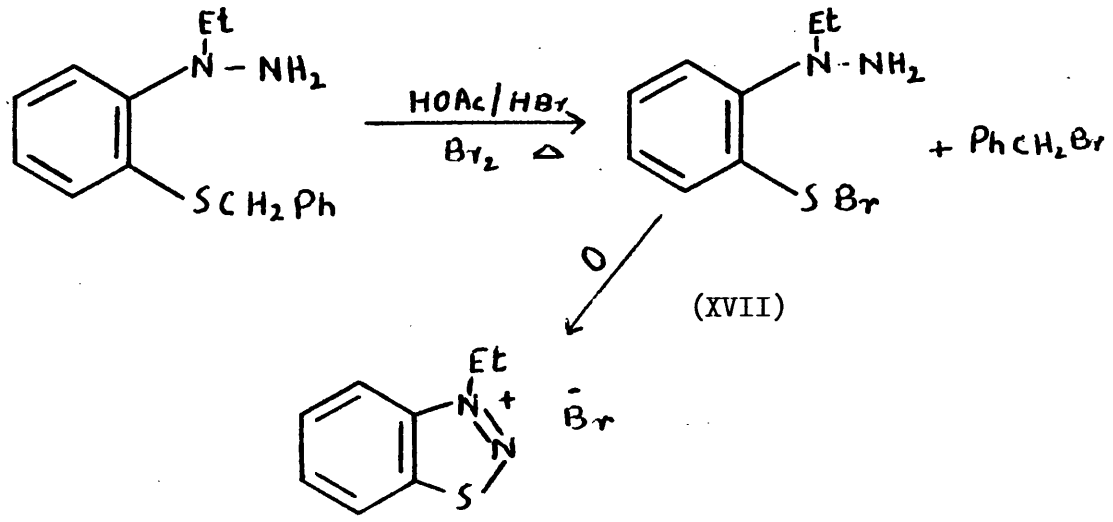
An experiment in which (XIV) was reacted with hydrogen bromide gas in the presence of acetic acid and acetic anhydride (protic conditions), gave N-ethyl-N-bromo-2-aminophenylbenzyl sulphide (XVI)(42.8%). The structure of (XVI) was supported by elemental analysis. Nucleophilic substitution had occurred. No ring closed product was formed.



(XVI)

Synthesis of 3-Ethyl-1, 2, 3-benzothiadiazolium Bromide (VII).—

N-Ethyl-2-hydrazinophenylbenzyl sulphide (VI) heated in acetic acid with hydrobromic acid (48%) and bromine, ring closed to give (VII)(88.8%) m.p. 189°. This showed no depression in melting point when mixed with an authentic sample, synthesised by direct quaternization, also the i.r. spectrum was identical with the i.r. spectrum of an authentic sample[66]. Evidently the reaction proceeded by debenzylation (benzyl bromide was evolved), followed by ring closure of the sulphenyl bromide (XVII) intermediate, accompanied by oxidation.



(VII)

EXPERIMENTAL

Preparation of 2-Aminophenylbenzyl Sulphide (X).-

Sodium wire (7.5 g., 0.3 atom) was suspended in dry dioxane (300 ml.). 2-Aminothiophenol (40 g., 0.32 mole) was added to the sodium-dioxane suspension. The reaction mixture was refluxed with stirring for 6 hr. The yellow colour of the solution changed to purple-white due to the formation of the sodium salt of 2-aminothiophenol. Benzyl chloride (40 g., 0.31 mole) was added slowly to the reaction mixture and immediately an exothermic reaction occurred. When all the benzyl chloride had been added, the mixture was stirred at room temperature for 4 hr. After filtration, dioxane was removed under reduced pressure and the residue was poured into ice water. The fawn solid after recrystallization (charcoal) from petroleum gave 2-aminophenylbenzyl sulphide (X), (40 g., 58%) m.p. 44-45° (lit.,[11-14] 43-45°).

ν max (KBr) 3410-3310 (NH_2) $cm.^{-1}$

2, 2' Dibenzylthioazobenzene.-

2-Aminophenylbenzyl sulphide (X) (2.8 g., 0.013 mole) and sodium hydride (1 g. in oil suspension) were placed in ether (50 ml.) and then monochloramine (0.6 g., 0.01 mole) was added. The mixture was stirred at room temperature for 4 hr., filtered and the filtrate concentrated under reduced pressure. The oily orange coloured residue was taken up in methylene chloride and chromatographed on alumina. The first petroleum eluate gave unreacted starting material 2-aminophenylbenzyl sulphide (X) (1.68 g.,60%), checked by comparing its m.p. and i.r. spectrum with those of an authentic sample. The chloroform eluate yielded 2, 2'-dibenzylthioazobenzene (XV) (200 mg.,

3.6%) m.p. 170^{d} (lit.[76] 223°)(Found: C, 72.76; H, 5.65; N, 6.56; S, 14.81. Calc. for $C_{26}H_{22}N_2S_2$: C, 73.13; H, 5.19; N, 6.56; S, 15.02%).

Methylation of 2-Aminophenylbenzyl Sulphide.-

(a) By dimethyl sulphate/alkali.

2-Aminophenylbenzyl sulphide (X) (4 g., 0.018 mole) was suspended in aqueous potassium hydroxide 2.5N (10 ml.). Dimethyl sulphate (2.3 g., 0.018 mole) was added to the above solution. The reaction mixture was stirred at 80° on a water bath for 2 hr., after which it was diluted with water and extracted with ether and the ether extract dried over magnesium sulphate. The ether was removed under reduced pressure, leaving a yellow oily residue of N-methyl-2-amino-phenylbenzyl sulphide (XI) (R=CH_3) (400 mg., 9.3%).

ν max (liquid) 3360 (>N-H), 3050, 2900, 2780, 1600 cm^{-1}.

(b) By methyl iodide.

2-Aminophenylbenzyl sulphide (X) (1g., 0.004 mole) was heated with methyl iodide (1.9 g., 0.013 mole) at 60° for 3 hr. The reaction mixture was shaken with ether (3 x 50 ml.) and the combined ether extracts dried over sodium sulphate. The removal of ether left a yellow oil, N-methyl-2-aminophenylbenzyl sulphide (XI) (R=CH_3) (0.053 g., 5%).

ν max (liquid) 3360 (>N-H), 3050, 2900, 2780, 1600 cm^{-1}, which was identical with the infra red spectrum of the product described in the previous experiment.

The ether insoluble residue possibly contained some poly methylated and quaternary products of 2-aminophenylbenzyl sulphide (X) An attempt to separate this mixture into its components by column chromatographic technique was not successful.

Ethylation of 2-Aminophenylbenzyl Sulphide (X) .-

(a) By triethylorthoformate.

Into a round bottomed flask (250 ml.) were placed 2-aminophenylbenzyl sulphide (X) (5 g., 0.023 mole), triethyl orthoformate (5 g., 0.03 mole) and concentrated sulphuric acid (0.9 g.). A column (30 x 2 cm.) packed with glass beads was attached to the flask. The flask was heated on oil bath at 115-120° to remove ethanol. After 1 hr. the temperature of the bath was maintained at 180° for 3 hr. The black gummy residue was vacuum distilled at 160°/0.01 mm. and the unreacted triethyl orthoformate was collected. The residue was chromatographed on alumina. Petroleum eluate gave N-ethyl-2-amino phenylbenzyl sulphide (XIII)(1.6 g., 28.4%).

ν max (liquid) 3375 (>N-H), 3060, 3030, 2970, 2930, 1590 cm^{-1}.

(b) By reduction of N-acetyl-2-aminophenylbenzyl sulphide (XII).

N-Acetyl-2-aminophenylbenzyl sulphide (XII)(1.192 g., 0.004 mole), in dry ether (40 ml.) was added slowly to lithium aluminium hydride (0.3 g., 0.009 mole) suspended in ether (20 ml.). After the addition was complete, the reaction mixture was stirred at room temperature for 6 hr. The complex was decomposed with water (10 ml.). The reaction product was extracted with ether. The ether extract after washing with water was dried over sodium sulphate. The solvent was evaporated under reduced pressure, when an oily residue of N-ethyl-2-aminophenylbenzyl sulphide (XIII)(1.08 g., 96.4%) was obtained, which was identical with the product from the previous experiment.

ν max (liquid) 3375 (>N-H), 3060, 3030, 2970, 2930, 1590 cm^{-1}.

N-Amination of N-Ethyl-2-Aminophenylbenzyl Sulphide (XIII).-

(a) By monochloramine.

Monochloramine (0.6 g., 0.01 mole) in ether was added to the solution of N-ethyl-2-aminophenylbenzyl sulphide (XIII)(2 g., 0.008 mole) in ether (30 ml.) and sodium hydride (0.6 g. in oil suspension). The reaction mixture was stirred at room temperature for 4 hr. The ether was removed under reduced pressure and the gummy residue dissolved in methanol and chromatographed on alumina. The methanol eluate gave a viscous, dark coloured oil N-ethyl-2-hydrazinophenyl benzyl sulphide (VI)(0.21 g., 10%).

ν max (liquid) 3360-3300, 3060, 3030, 2970, 2930, 1600 cm^{-1}.

(b) By hydroxylamine-O-sulphonic acid.

N-Ethyl-2-aminophenylbenzyl sulphide (XIII)(2 g., 0.008 mole) was suspended in aqueous potassium hydroxide (1.6 g. in 10 ml. water) and hydroxylamine-O-sulphonic acid (0.96 g.) was added portion-wise to the stirring alkaline solution. When the addition was complete, the mixture was heated at 60° for 4 hr. After extraction with ether and benzene, the combined extracts were dried over sodium sulphate. The solvent was evaporated under reduced pressure to leave a viscous residue of N-ethyl-2-hydrazinophenylbenzyl sulphide (105 mg., 5%).

ν max (liquid) 3370, 3060, 3030, 2970-2930, 1590 cm^{-1}.

N-Nitrosylation of N-Ethyl-2-aminophenylbenzyl Sulphide.-

(a) By nitrosyl bromide.

N-Ethyl-2-aminophenylbenzyl sulphide (XIII)(3 g., 0.012 mole) in ether was added to the nitrosyl bromide, prepared by passing dry nitric oxide gas (made from acidic ferrous sulphate and sodium nitrite) into bromine (2 ml.) dissolved in ether (10 ml.). The

reaction mixture was stirred at room temperature for 4 hr. and for a further 2 hr. at 30°. A dark gummy residue was obtained which could not be purified and was not studied further.

(b) By nitrous acid.

N-Ethyl-2-aminophenylbenzyl sulphide (XIII)(14.5 g., 0.059 mole) was suspended in hydrochloric acid (2 g.) and the acid solution was diluted with water (15 ml.). To this suspension was added aqueous sodium nitrite (3.4 g., 0.048 mole in water 20 ml.). The reaction mixture was stirred at 50° on a water bath for 3 hr. The mixture was diluted with water, extracted with ether, the ether extract washed thoroughly with water and finally dried over magnesium sulphate. The solvent was evaporated under reduced pressure. Crystallization with petroleum yielded N-ethyl-N-nitroso-2-amino phenylbenzyl sulphide (XIV) (9g., 56%) m.p. 45° (Found: C, 66.05; H, 5.84; N, 10.31; S, 11.80. $C_{15}H_{16}N_2OS$ requires C, 66.23; H, 5.93; N, 10.30; S, 11.79%).

ν max (KBr) 3060, 3030, 2980, 2940, 2930, 1445 and 1428 (-N=O) cm^{-1}.

nmr ($CDCl_3$) τ 9.0 (triplet, 3H, CH_3) J=7 cps,
5.95 (quartet, 4H, two CH_2 groups) J=7 cps,
2.75 (9H, aromatic).

Reduction of N-Ethyl-N-nitroso-2-Aminophenylbenzyl Sulphide (XIV).-

(a) By sodium dithionite ($Na_2S_2O_4$).

N-Ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV)(1g., 0.0036 mole) was dissolved in 20% sodium hydroxide (10 ml.) and ethanol (15 ml.). The mixture was stirred under nitrogen at 58° for 30 min.

Then sodium dithionite (1.3 g., 0.007 mole) was added in one portion to the warm solution. After the reaction mixture had refluxed for 12 hr. it was extracted with ether. The extract was dried over magnesium sulphate and the ether removed under reduced pressure. A dark brown, gummy residue of N-ethyl-2-hydrazinophenylbenzyl sulphide (VI)(0.210 g., 10%) was obtained.

ν max (liquid) 3370, 3060, 3030, 2970, 1590 cm^{-1}.

(b) By palladium on charcoal and Adam's catalyst.

N-Ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV) (2g., 0.0073 mole) was dissolved in 2N absolute ethanolic hydrochloric acid (20ml.). Palladium on charcoal (150mg.) and Adam's catalyst (50mg.) were added and the mixture shaken with hydrogen for 72 hr. (uptake of hydrogen was 200ml.). The reaction mixture was filtered and the alcoholic filtrate concentrated under reduced pressure. It yielded N-ethyl-2-hydrazinophenylbenzyl sulphide (VI)(420 mg., 10%).

ν max (liquid) 3370, 3060, 3030, 2970, 1590 cm^{-1}.

(c) By lithium aluminium hydride.

N-Ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV)(2.48 g., 0.009 mole) in dry ether (20ml.) was added to the suspension of lithium aluminium hydride (0.8 g.) in dry ether (20 ml.). The reaction mixture was stirred for 6 hr. at 30°. The complex was decomposed by adding water (5ml.) and the mixture filtered. The residue was washed with ether. The filtrate was dried over sodium sulphate and the solvent removed under reduced pressure to yield N-ethyl-2-hydrazinophenylbenzyl sulphide (VI)(2.25 g., 95%).

ν max (liquid) 3400-3320, 3060, 3020, 2970, 2930, 1590 cm^{-1}.

N-Ethyl-N-Bromo-2-Aminophenylbenzyl Sulphide (XVI).-

N-Ethyl-N-nitroso-2-aminophenylbenzyl sulphide (XIV)(3 g., 0.011 mole) was dissolved in acetic anhydride (10 ml.)and glacial acetic acid (30 ml.). Anhydrous hydrogen bromide gas (made by the action of bromine on tetralin)[42] was passed into the above solution. The reaction mixture was stirred at room temperature for 1 hr. during which the colour changed from yellow to purple green, accompanied by the evolution of heat. Then the mixture was refluxed for 4 hr.. and finally stirred at room temperature for 48 hr. The acetic anhydride and acetic acid were evaporated off on a water bath. After the removal of solvent a brownish residue was left. This gummy residue was boiled with ethanol. The ethanolic solution was decolourised with charcoal, and on crystallization yielded N-ethyl-N-bromo-2-amino — phenylbenzyl sulphide (XVI)(1.5 g., 42.2%) m.p. 112° (from ether). (Found: C, 57.44; H, 4.96; N, 4.70; Br, 25.09. $C_{15}H_{16}NBrS$ requires: C, 55.95; H, 5.01; N, 4.35; Br, 24.82; S, 9.96%).

ν_{max} (KBr) 3080, 3060, 2980, 2920, 2780 cm^{-1}.

Synthesis of 3-Ethyl-1, 2, 3-Benzothiadiazolium Bromide (VII).-

N-Ethyl-2-hydrazinophenylbenzyl sulphide (VI)(1 g., 0.0038 mole) was added to glacial acetic acid (12 ml.) and the mixture refluxed. Bromine (1 ml.) in hydrobromic acid 48% (5 ml.) was added in one portion to the boiling solution, and the reaction mixture refluxed for 1.5 hr. It was diluted with water, and the aqueous layer separated from benzyl bromide. The aqueous layer was boiled with charcoal and filtered. The filtrate was concentrated on a water bath,

the yellow residue taken up in ethanol and recrystallized from ethanol, which yielded 3-ethyl-1, 2, 3-benzothiadiazolium bromide (VII)(0.8 g., 89%) m.p. 189° (lit.[66] 190°).

ν max (KBr) 3070, 3000, 2940 cm^{-1},

identical with the i.r. spectrum of an authentic sample[66], obtained by direct quaternization of 1, 2, 3-benzothiadiazole.

SECTION III

INTRODUCTION

Whilst attempting to prepare the hydrazine of 2-aminophenylbenzyl sulphide by the reaction of the latter with ethereal chloramine (N-amination of 2-aminophenylbenzyl sulphide), cis-2,2'-dibenzylthioazobenzene was formed in low yield (Section II). It was thought to extend and apply this reaction to other aromatic primary amines, aryl and alicyclic alcohols and to study the effects of electron withdrawing or donating groups on the aromatic nucleus.

Though the chemistry of chloramine has been thoroughly studied, no comprehensive review of chloramine has been published, although the specific aspects of the chemistry of chloramine have been reviewed,[77-82] for example the Raschig synthesis[83] of hydrazine. Recently Sale[122] has reviewed the N-amination reactions of chloramine. A brief outline of the chemistry of chloramine (preparation, reactions and uses) and methods for the oxidation of aniline and substituted anilines to azobenzenes are described in this introduction.

Preparation and Hydrolysis of Chloramine.-

Chloramine was first prepared by Raschig[83] in 1907 by the reaction of ammonia with sodium hypochlorite in dilute aqueous solutions at 0°.

$$NH_3 + NaOCl \longrightarrow NH_2Cl + NaOH$$

The process was modified later,[77,84,85] and nearly quantitative yields of chloramine were obtained by using three equivalents of ammonia to one of hypochlorite. The addition of ammonium chloride suppressed the formation of sodium hydroxide which decomposed the chloramine.

$$NH_4Cl + NaOCl \xrightarrow{\text{base}} NH_2Cl + NaCl + H_2O$$

Kinetic studies[86] of the rate of reaction of aqueous chlorine with ammonia, methylamine, or dimethylamine showed that chloramine was formed by an S_N2 mechanism in accordance with the equation:

$$HOCl + NH_3 \longrightarrow NH_2Cl + H_2O$$

The reaction was base catalysed, the pH of the solution being critical.[87,88] Chloramine is formed above pH 8.5, dichloramine between pH 4.4 and 8.5 and nitrogen trichloride below pH 4.4.

Aqueous solutions of chloramine (12%) free from impurities can be obtained by distillation at 15-25 mm. of dilute aqueous solutions prepared by the reaction of ammonia and hypochlorite.[89] Dehydration of the aqueous distillate with potassium carbonate gave pure anhydrous chloramine,[90] m.p. -60°, which decomposed explosively at -50°. Anhydrous ethereal chloramine solutions can be obtained by extraction of aqueous solutions and drying the organic layer with calcium chloride.[79,90] The distribution coefficient[90] between ether and water is almost one. Gas-phase chlorination of ammonia[91] and the reaction of either gaseous chlorine or of a solution in carbon tetrachloride with liquid ammonia[91b,92] gave anhydrous chloramine (95%). Excess of ammonia was used to prevent further chlorination and the chlorine was diluted with nitrogen. Organic halogen compounds, for example t-butyl hypochlorite,[93] and N-chlorosuccinimide,[94] when treated with aqueous ammonia have also been reported to give chloramine; the yield depends upon the molar ratios of the reactants and the presence of a permanent base.

Sisler and Batey[95] have prepared chloramine by the reaction of nitryl chloride (NO_2Cl) with ammonia. Hydrolysis of N, N'-dichlorourea[96] and potassium N-chloroaminosulphonate[97] ($ClNH_2SO_3K$) are

also reported to yield chloramine.

Aqueous solutions of chloramine are reasonably stable when made slightly basic with ammonia, but decompose readily in acidic solutions,[90,98] via dichloramine and nitrogen trichloride, to give ammonium chloride, nitrogen and hydrochloric acid which further catalyses the decomposition. Markwald and Willie[90] have reported that concentrated hydrochloric acid reacted with chloramine to give ammonium chloride and chlorine. The decomposition of chloramine in basic media is very complex. Raschig examined the final products of decomposition of chloramine in alkaline solution, and found nitrogen, ammonia and chloride ions in accord with the equation:

$$3NH_2Cl \xrightarrow{\bar{O}H} N_2 + 3\bar{C}l + NH_3 + 3H_2O$$

The primary products of hydrolysis of chloramine suggested were either hypochlorite ions and ammonia, or hydroxylamine and chloride ions. Corbett, Metcalf and Soper[88] have shown that hydrolysis of chloramine to hypochlorite and ammonia is reversible and have measured the equilibrium constant of this reaction.

$$NH_2Cl + \bar{O}H \rightleftharpoons NH_3 + O\bar{C}l$$

McCoy[99] has shown that initial step of the reaction is the formation of hydroxylamine

$$NH_2Cl + \bar{O}H \longrightarrow NH_2OH + \bar{C}l$$

which is then oxidized by chloramine.

$$NH_2Cl + 2NH_2OH + \bar{O}H \longrightarrow NH_3 + N_2 + 3H_2O + \bar{C}l$$

A comprehensive investigation[100] of the hydrolysis of chloramine in alkaline solutions from pH 11.55 upwards using molar sodium hydroxide or potassium hydroxide found large rate increases above

pH 14. The products identified were N_2, N_2O, N_2H_4, $N_2O_2^-$, $O{=}NO{-}O^-$ and NH_2OH; nitrogen and nitrous oxide being the major products. The suggested[88] formation of hypochlorite during the hydrolysis of chloramine, could not be confirmed by Anbar and Yagil[100], who found that the addition of ammonia caused an increase rather than a decrease in rate of disappearance of chloramine.

Reactions of Chloramine.-

(a) With Ammonia.

During the preparation of chloramine by the reaction of ammonia with sodium hypochlorite, Raschig[83] noticed that further treatment of ammonia with chloramine yielded hydrazine and thus chloramine was first used as an aminating agent. The mechanism of this reaction was the subject of much debate, and many papers have been published providing conflicting evidence. Raschig originally proposed the initial decomposition of chloramine to form nitrene (NH), followed by attack on ammonia to give hydrazine. Audrieth et al[93,94] suggested that the active intermediate in the hydrazine synthesis is the chloramide ion, ($\bar{N}HCl$). This conjugate base either decomposed to give imene or alternatively attacked ammonia directly.

$$NHCl^- \longrightarrow \ddot{H}\ddot{N}: + Cl^-$$

$$\ddot{H}\ddot{N}: + NH_3 \longrightarrow N_2H_4$$

or $$HNCl^- + NH_3 \longrightarrow N_2H_4 + Cl^-$$

Bodenstein[101] proposed that direct substitution occurred, as he found the reaction to be first order with respect to both reactants (at pH~11). These results were confirmed by Cahn and Powell[102], who showed that chloramine reacted much faster with hydrazine than with

ammonia. Sisler[103] and Audrieth[104] indicated that an added base was not essential for the formation of hydrazine and obtained high yields (80%) by passing gaseous chlorine into a cold solution of aqueous ammonia. Chlorine diluted with nitrogen also gave hydrazine (18%) with aqueous ammonia.

Anbar and Yagil[105] studied the formation of hydrazine under a variety of conditions and showed that:

(1) The reaction is first order in both chloramine and ammonia.

(2) Low concentrations of chloramine and high concentrations of ammonia give maximum yields of hydrazine.

(3) The reaction is independent of base between pH 11 and 14. Above pH 14 the reaction is base catalysed but the yield of hydrazine falls due to competing hydrolysis of chloramine. However, for a given pH the rate of reaction to give hydrazine is still faster than the rate of hydrolysis.

(4) Addition of sodium chloride, gelatin or oxygen to the pure reaction mixture had negligible effects on the rate of reaction.

They therefore considered that two mechanisms (A) and (B) were in operation.

(A) Base - independent between pH 10 and 14:

$$NH_3 + NH_2Cl \longrightarrow \overset{+}{N}H_3NH_2 + \overset{-}{Cl} \qquad \text{(slow)}$$

$$\overset{+}{N}H_3NH_2 + \overset{-}{O}H \longrightarrow N_2H_4 + H_2O \qquad \text{(fast)}$$

(B) Base - catalysed, involving attack of ammonia on the chloramide ion:

$$NH_2Cl + \overset{-}{O}H \rightleftharpoons \overset{-}{N}HCl + H_2O \qquad \text{(fast)}$$

$$NH_3 + \overset{-}{N}HCl \longrightarrow \overset{+}{N}H_3\overset{-}{N}H + \overset{-}{Cl} \qquad \text{(slow)}$$

$$\overset{+}{N}H_3.\overset{-}{N}H \longrightarrow N_2H_4 \qquad \text{(fast)}$$

However mechanism (B) was disregarded (see (b) With Amines).

(b) With Amines.

Chloramine has been reported to react with amines, mostly aliphatic and a few alicyclic, to give the corresponding hydrazines. Audrieth and Diamond[106] in 1954 extended the reaction of amine and chloramine, analogous to the Raschig systhesis (NH_3 + $ClNH_2$) and found that chloramine under alkaline conditions reacted with methyl-, ethyl-, n-propyl-, isopropyl-, n-butyl-, isobutyl- and t-butyl-amine and isolated the corresponding hydrazines. The yield of hydrazine depended on the molar ratio of amine to chloramine, the presence of metal deactivators (gelatin) and the presence of a permanent base.

Anbar and Yagil[105] studied the kinetics of the reaction of aliphatic primary, secondary and tertiary amines with aqueous chloramine and found the reaction to be first order in both amine and chloramine in the base - independent and in the base - catalysed reaction. The mechanisms suggested were analogous to that of chloramine with aqueous ammonia.

The alternative base-catalysed mechanism:

$$\bar{O}H + R_2NH \longrightarrow R_2\bar{N} + H_2O \qquad \text{(fast)}$$

$$R_2\bar{N} + NH_2Cl \longrightarrow R_2N.NH_2 + \bar{C}l \qquad \text{(slow)}$$

was discounted because trimethylamine gave similar kinetic results to methylamine and dimethylamine. However, although it was shown that a reaction occurred between trimethylamine and chloramine, the products were never isolated and the possibility of an alternative reaction occurring other than amination, however unlikely this may seem, must

still be considered.

Audrieth et al.[107,85] extended the amine-chloramine reaction and showed that n-hexylamine, cyclohexylamine, allylamine, ethanolamine, ethylenediamine and morpholine reacted with chloramine under alkaline conditions and gave the corresponding hydrazines. N-Dialkylhydrazines[85] $R_2N\text{-}NH_2$ ($R=CH_3$, C_2H_5, n-C_3H_7 and n-C_4H_9) were also prepared by reaction of the appropriate amines with chloramine. These authors found that primary amines gave the corresponding hydrazines in good yields (52-75%); the nature of the alkyl group had very little effect and even amines containing other functional groups, such as ethanolamine, ethylenediamine, and allylamine, gave good yields of hydrazines.

Omietanski et al.[108] in 1956 showed that chloramine, produced by the gas phase reaction of chlorine and ammonia, reacted with anhydrous primary and secondary amines in the absence of permanent base, or other additive, to give N-substituted hydrazines in good yield. Methyl-, ethyl-, isopropyl-, unsymetrical dimethyl-, and unsymetrical di-isopropyl-hydrazines have been prepared under the above conditions.

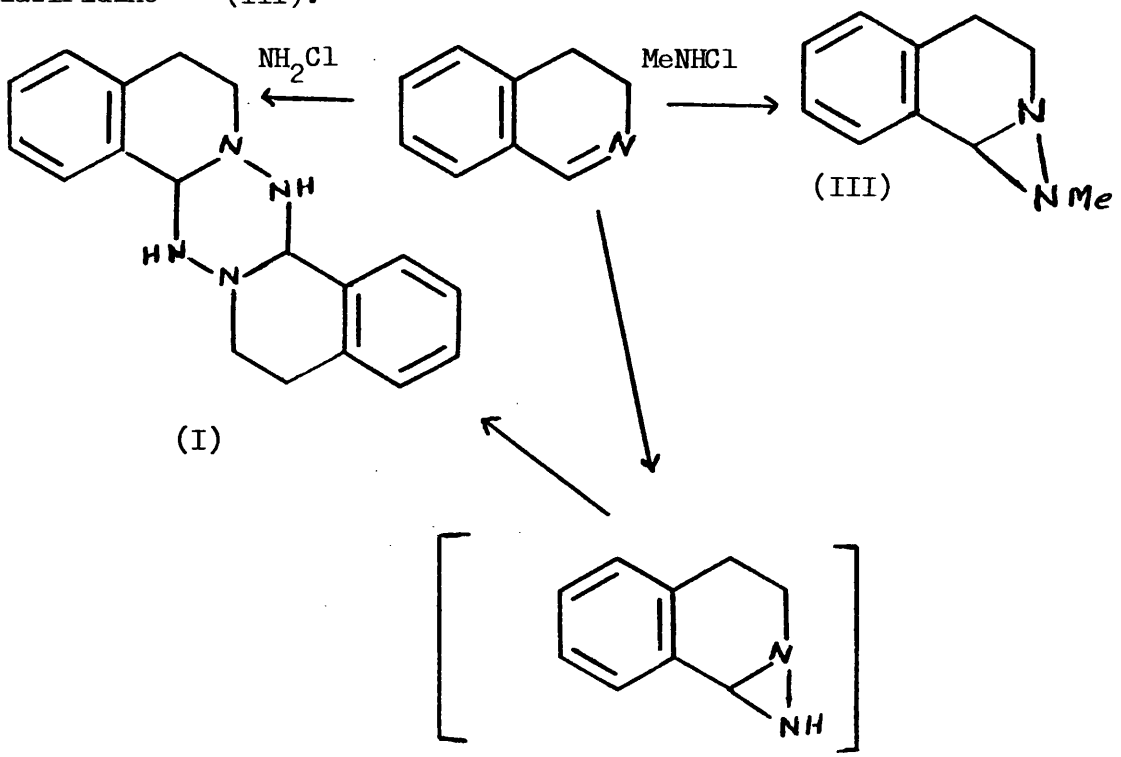
Sisler et al.[109] extended this reaction and showed that bubbling a chloramine-ammonia mixture into primary, or secondary amines, imines, imides and amides gave the corresponding hydrazine in moderate yield. Piperidine, cyclohexylamine, methylamine and n-butylamine have been reported to form hydrazines[109]. Although the competing reaction of hydrazine formation occurred, better yields were obtained with ammonia present, since ammonium chloride rather than the amine hydrochloride was then precipitated. Under similar conditions pure aniline[110] gave phenylhydrazine (46%) at room temperature.

When diethylamine[108] was treated in an analogous manner none

of the expected 1, 1-diethylhydrazine was obtained, and the products were ethylhydrazine, ammonium chloride and diethylamine hydrochloride. Aqueous chloramine gave the expected product however[85]. No explanation for this very unusual reaction was offered.

(c) With Schiff bases.

Schiff bases react with chloramine to give diaziridines. Schmitz[111] treated 3, 4-dihydroisoquinoline with aqueous methanolic chloramine at room temperature and isolated the dimeric adduct (1). He showed that the diaziridine (II) was initially formed and when methylchloramine was used, was able to isolate the substituted diaziridine[112] (III).



The reaction was found to be generally applicable to aliphatic Schiff bases derived from aldehydes, ketones and cyclic ketones[113,114].

(d) With diazonium chlorides and oximes.

Forster[115] showed that the treatment of diazonium salts and

oximes with aqueous chloramine yielded azides and diazo compounds respectively. Thus diazotised aniline and p-nitroaniline with aqueous chloramine gave phenylazide and p-nitrophenylazide respectively.

(e) With alcohols.

Truitt et al[116], in an attempt to prepare O-amino compounds by the action of ethereal chloramine with sodium alcoholates in cold benzene solution, found that only benzyl alcohol and β-phenoxyethanol gave (1-5%) O-amino compounds. iso-Amyl, cyclohexyl, β-phenyl ethyl and 4-methoxybenzyl alcohols did not react, and hence these authors[116] could not generalise this reaction. Theilacker and Ebbe[117] found that the reaction was generally applicable and reasonable yields of the O-hydroxylamines could be obtained when the alcohol and its sodium salt were treated with ethereal chloramine at 80°.

Oxidation of Aniline and Substituted Anilines.-

Aniline and substituted anilines have been oxidised to the corresponding trans-azobenzenes. The following is a brief account of the oxidising agents which have been employed for this purpose.

(a) By manganese dioxide.

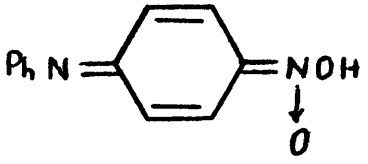
Manganese dioxide suspended in benzene under reflux has been used for the oxidation of aniline and substituted anilines to azobenzenes. Pratt and McGoven[118] oxidized p-chloroaniline, p-phenylaniline, p-toludine, p-anisidine, p-nitroaniline, γ-aminopyridine and p-cyanoaniline to azo compounds. Nitroanilines (o, m, p) gave low yields of corresponding azo compound. A free radical mechanism[118] was proposed:

$$RCH_2NHR_1 + \overset{+4}{O}{=}Mn{=}O \longrightarrow RCH_2\dot{N}R_1 + OHMn{=}\overset{+3}{O}$$

$$RCH_2\dot{N}R_1 + OHMn{=}\overset{+3}{O} \longrightarrow RCH{=}NR_1 + \overset{+2}{O}HMnOH$$

$$\overset{+2}{O}HMnOH \longrightarrow \overset{+2}{M}nO + H_2O$$

Wheeler and Gozaleg[119] have also reported that manganese dioxide oxidized aniline, p-fluoro-, p-chloro-, p-bromo-, p-iodo-aniline, p-anisidine, p-biphenylamine, m-chloro-, o-fluoro-, o-iodo and o-ethyl-aniline and o-anisidine. However, nitroanilines were recovered unchanged. The failure of the nitroanilines to oxidise was attributed to adsorption on the active oxidation centres[119] in manganese dioxide, and the presence of a tautomeric form[118] (IV).



(IV)

(b) By Phenyl iodosoacetate.

Pausacker[120] has used the phenyl iodosoacetate for the oxidation of aromatic amines to azo-compounds. Aniline, o-, m-, p-toluidine, o-, m-, p-chloroaniline, o-anisidine and m-, p-nitroaniline gave the corresponding azobenzene in good yield, but o-nitroaniline was converted to benzofurazan oxide.

A free radical mechanism was proposed.

$$2PhI(OAc)_2 + 2ArNH_2 \rightleftharpoons 2PhI(OAc)NHAr + 2AcOH$$

$$2PhI(OAc)NHAr \longrightarrow 2ArNH^{\bullet} + 2PhI(OAc)^{\bullet}$$

$$2ArNH^{\bullet} \longrightarrow ArNHNHAr$$

$$ArNHNHAr + 2PhI(OAc)^{\bullet} \longrightarrow ArN{=}NAr + 2AcOH + 2PhI$$

(c) By lead tetraacetate.

Pausacker and Scroggie[121] used lead tetraacetate in acetic

acid at room temperature for the preparation of azobenzenes from substituted anilines. A free radical mechanism has also been proposed[121] for this reaction.

$$2Pb(OAc)_4 + 2ArNH_2 \rightleftharpoons 2Pb(OAc)_3NHAr + 2AcOH$$

$$2Pb(OAc)_3NHAr \longrightarrow 2ArN\dot{H} + 2Pb(OAc)_3^{\bullet}$$

$$2ArN\dot{H} \longrightarrow ArNHNHAr$$

$$ArNHNHAr + 2Pb(OAc)_3^{\bullet} \longrightarrow ArN{=}NAr + 2AcOH + 2Pb(OAc)_2$$

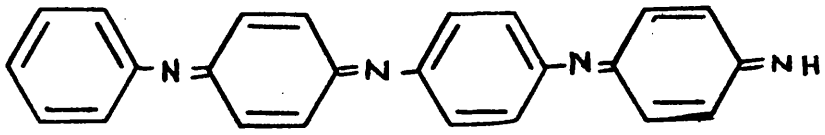
Conversion of trans to cis-Azobenzenes by Photolysis.-

Cook[123] has shown the presence of some of the cis-isomers in irradiated solutions of trans-azobenzenes in petroleum, but was unable to isolate them except for cis-azobenzene, cis-benzene-azo-p-toluene and cis-p p'azotoluene in very low yields. He irradiated petroleum solutions of azobenzene, benzene-azo-p-toluene, o o'-, m, m-, and p-p'-azotoluene, p-benzeneazophenol, p-aminoazobenzene, p-benzeneazo-phenetole, p-chloroazobenzene and p-cyanoazobenzene. The separation of a few of the cis-isomers was achieved on an alumina column. The trans-isomer was eluted first and then the more polar cis-isomer. Cook found that in many cases the cis-isomer rapidly reverted back to the trans- form and the change was complete within two days at room temperature in the absence of light.

DISCUSSION OF RESULTS

Oxidation of Amines.-

Aniline, hydrazobenzene and phenylhydrazine reacted with ethereal chloramine yielded trans-azobenzene (50, 90 and 20% respectively); a quantitative amount of ammonium chloride was isolated in each case. It was observed that the reaction mixture acquired an orange colour during the evaporation of the solvent under reduced pressure and this colour deepened as the solution became more concentrated. Then, when the residue had stood for a few moments at room temperature, an exothermic reaction, with darkening of the colour took place. In the case of aniline this exothermic reaction gave a blue amorphous powder with no distinct m.p., probably a polymeric quinonediimine (V) or a partially reduced form of this[124].



(V)

In an experiment when aniline was treated with ethereal chloramine for 4 days, similar results were obtained. However when methylene chloride was used instead of ether, the exothermic phase did not occur, the yield of azobenzene was reduced to a half and no blue compound was formed.

Oxidation of Substituted Anilines.-

(i) p-Toluidine.

p-Toluidine under the same conditions gave both trans- and cis-azotoluene in the ratio of 2:1 respectively. These were

separated on an alumina column, the trans- isomer eluted first and then the cis- isomer. The i.r. spectrum of the cis- isomer differed slightly from that of the trans- isomer, and both compounds had different u.v. spectra and m.p's. The behaviour of the two isomers on the chromatographic column was found to be identical with that reported by Cook.[123]

(ii) p-Chloroaniline.

p-Chloroaniline with chloramine gave trans-p-chloroazobenzene and cis-p-chloroazobenzene in the ratio of 1:1. The same order of elution from the column was observed. The two had different colours and m.p.'s. Elemental analysis of cis-isomer gave a molecular formula of $C_{12}H_8N_2Cl$. The i.r. spectra of the two isomers were slightly different. The structure of the two isomers was supported by u.v. spectra.

(iii) p-(Dimethylamino) aniline.

The reaction of p-(dimethylamino) aniline and chloramine under the above conditions, resulted in the formation of trans- and cis-azo compounds in the ratio of 5:6 respectively and a dark blue amorphous polymeric compound. The trans- isomer was confirmed by elemental analysis and by comparing its m.p. with literature[127] values. The second compound was thought to be the cis- isomer and this was supported by its u.v. spectrum and elemental analysis. The dark red cis- isomer melted at a lower temperature than the orange trans- isomer.

(iv) 2-Aminodiphenyl.

2-Aminodiphenyl reacted with chloramine; the t.l.c. of the reaction mixture showed two spots, corresponding to trans- and cis- isomer and a long streak. The chromatogram did not show a spot

corresponding to carbazole. The two isomers were separated on an alumina column. The trans- isomer (red) was eluted first and then the cis- isomer (dark red). The trans- isomer had the same m.p. as reported in literature,[128] the cis- isomer had a lower m.p. than the trans- form, moreover its molecular formula was confirmed by elemental analysis. Equal amounts of the two isomers were isolated.

(v) p-Ethoxyaniline.

p-Ethoxyaniline yielded only the trans- isomer in moderate yield. This was confirmed by comparing its m.p. with that of literature value. Cook[123] also isolated only the trans- isomer. Although he obtained indication of a cis- form, he found that this rapidly reverted to the more stable trans- isomer.

(vi) Benzylamine.

Benzylamine was oxidized by chloramine under the above conditions and yielded benzylamine hydrochloride, confirmed by elemental analysis and m.p., and benzaldehyde, confirmed by preparing its 2, 4-dinitrophenylhydrazone.

Quantitative amounts of ammonium chloride were isolated in all of the above experiments.

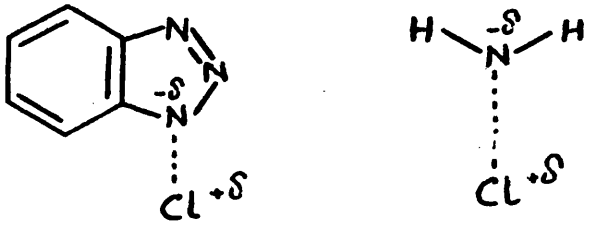
(vii) Attempted oxidation.

p-Nitroaniline, 2, 4, 6-tribromo-aniline, benzamide, acetanilide, 2-aminopyridine and t-butylamine did not react with ethereal chloramine and 95% of unreacted starting material was recovered in each case.

The particular value of this method of oxidation of aromatic primary amines to azobenzenes is that it provides a convenient route to certain cis-azobenzenes that are otherwise very difficult to obtain.

Probably other substituted anilines, carrying electron donating groups on the benzene ring can be oxidized with chloramine to give cis-azobenzenes. This is supported by the results obtained in the present work, for example p-toluidine, p-amino-N, N-dimethylaniline p-chloroaniline and 2-aminodiphenyl, yielded cis- and trans- isomers.

It was found that p-nitroaniline gave neither cis- nor trans-azobenzene. Other workers[118,119] also found that the nitroanilines were resistant to oxidation. The results obtained in the present work indicate that chloramine is behaving as an oxidising agent. 1-Chlorobenzotriazole, which has a similar electronic distribution as chloramine



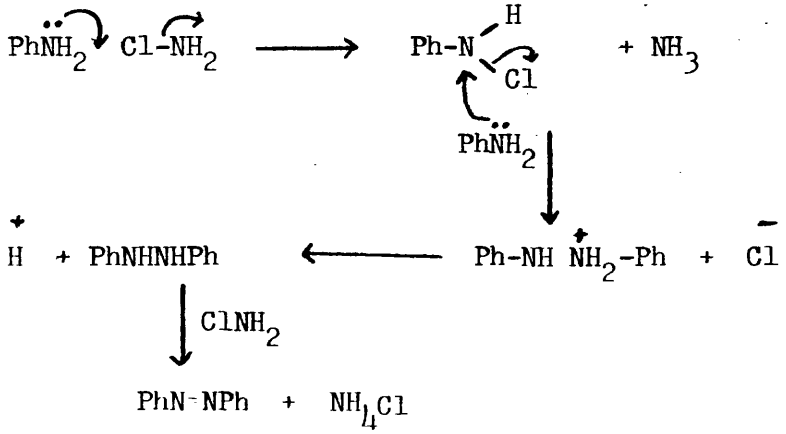
has recently been employed[125] to oxidize alcohols and hydrazo compounds. Chloramine might be expected to behave in a similar fashion.

Mechanism of the Chloramine - Oxidation of Amines.-

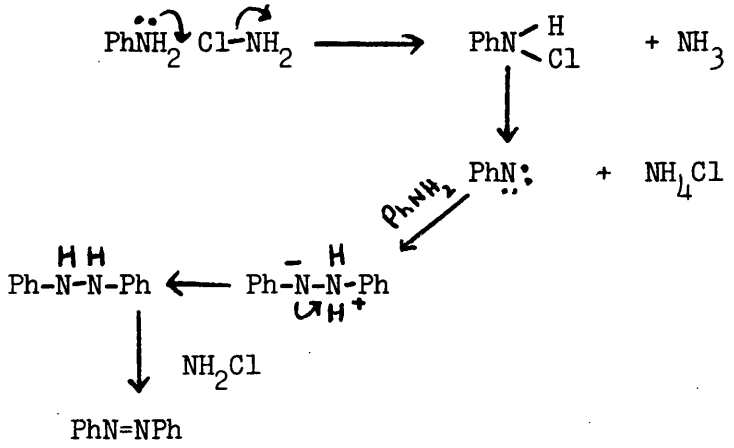
$$2PhNH_2 + 2NH_2Cl \longrightarrow PhN{=}NPh + 2NH_4Cl$$

The reaction mechanism may involve (a) protonated hydrazobenzene (b) nitrene or (c) hydrazine intermediate according to schemes:

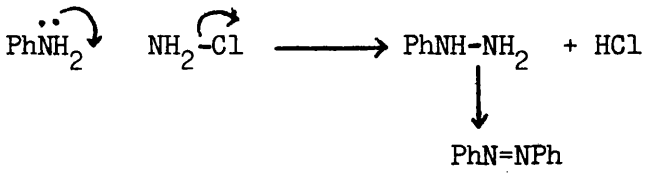
(a) Protonated hydrazobenzene.



(b) Nitrene intermediate.



(c) Hydrazine intermediate.



The possibility of nitrene intermediate does not seem likely, since the reaction of 2-aminodiphenyl and chloramine gave only cis and trans 2,2'-azobiphenyl and no carbazole. The mechanism with a hydrazine intermediate seems improbable, since the reaction conditions are not sufficiently basic and because phenylhydrazine on chloramine oxidation yielded only 20% azobenzene.

Mechanism (a) which involves protonated hydrazobenzene seems more likely. The final step of the suggested mechanism (a) receives some support from the ready reaction of hydrazobenzene and chloramine to give a high yield of azobenzene. In view of this facile oxidation, it was not surprising that the reaction of aniline with a half molar quantity of chloramine did not give any hydrazobenzene, but instead azobenzene and unchanged aniline in equal amounts.

The presence of electron donating groups ortho or para to the amino group should make it more susceptible to oxidation, whilst electron withdrawing groups either on the aromatic nucleus, or on the nitrogen should make the oxidation of the amine more difficult. p-Toluidine was easily oxidised to 4,4'-dimethylazobenzene, separated as cis and trans isomers (14% and 28% respectively) by column chromatography.

Similarly p-chloroaniline gave cis and trans 4,4'-dichloroazobenzene (20% of each); p-amino-N, N-dimethylaniline gave both isomers of 4,4'-di(dimethylamino)azobenzene (10% of each); whilst p-ethoxyaniline was oxidised solely to trans 4,4'-diethoxyazobenzene (30%). These yields were all lower than that from aniline itself; this may be explained by the greater susceptibility of these compounds to further oxidation giving the coloured, polymeric quinonediimine type of compounds. In all cases strong exothermic reactions took place on concentration. In contrast p-nitroaniline reacted up to a maximum of 5% and 2-aminopyridine, 2, 4, 6-tribromoaniline, benzamide and acetanilide failed to react at all. This shows that electron withdrawing groups inhibit the oxidation of the aromatic amino group by chloramine. In the case of 2, 4, 6-tribromoaniline steric inhibition probably occurs. Attempts to obtain azo compounds from benzylamine and t-butylamine were unsuccessful.

Oxidation of Alcohols.-

The results obtained from the reaction of aniline and substituted anilines with chloramine implied that the reaction might be extended to the oxidation of alcohols. Furthermore the use of

1-chlorobenzotriazole as an oxidant for alcohols under mild conditions made it probable that chloramine would behave in a similar manner. Following alcohols were reacted with chloramine.

(i) Benzyl alcohol.

When benzyl alcohol was treated with ethereal chloramine solution, an exothermic reaction occurred at the last stage of solvent removal under reduced pressure. Benzaldehyde was isolated in high yield as its 2, 4-dinitrophenylhydrazone. A quantitative amount of ammonium chloride was also isolated.

(ii) Di-phenylmethanol.

Diphenylmethanol treated in a like manner was oxidized by chloramine and gave benzophenone in high yield and ammonium chloride. The structure of the benzophenone was confirmed by m.p., i.r. and by preparation of its 2, 4-dinitrophenylhydrazone.

(iii) Cyclohexanol.

Cyclohexanol when treated with chloramine gave ammonium chloride and some cyclohexanone. The presence of cyclohexanone in the reaction mixture was indicated by its i.r. spectrum. The i.r. spectrum of the oily product showed both (OH) and (>C=O) peaks.

(iv) Attempted oxidation.

Cholesterol and allyl alcohol did not react with chloramine under the usual conditions and unreacted starting material (90%) was recovered in both cases.

EXPERIMENTAL

Ethereal Chloramine.-

Powdered ammonium chloride (15.0 g., 0.27 mole) was suspended in ether (500 ml.) and cooled to -10°. Concentrated aqueous ammonia (26 ml.) was added to the mixture which was then stirred vigorously while commercial aqueous sodium hypochlorite (140 ml.) was added in small portions over 5-10 min., keeping the internal temperature between -15° and -10°. The ethereal layer was separated, washed with saturated aqueous sodium chloride solution (175 ml.) and dried over granulated calcium chloride for 1 hr. at -15°. Fresh solutions of ethereal chloramine were made for each experiment. The chloramine was estimated by iodometric titration: Potassium iodide (10g.) dissolved in water (150 ml.) containing concentrated hydrochloric acid (2 ml.) was treated with a 10 ml. aliquot of ethereal chloramine. After shaking for 20 min., the ether was removed from the mixture by warming and the cooled solution was then made up to 250 ml. This solution was titrated against 5 ml. aliquots of standard N/10 sodium thiosulphate solution using starch as indicator. The ethereal chloramine solutions were normally in the range of 0.1 to 0.3 molar.

Oxidation of Amines.-

(i) Aniline.

Chloramine in ether (500 ml. of 0.1M solution, 0.05 mole) at -10° was added to freshly redistilled aniline (3.1 g., 0.03 mole). The reaction mixture was stirred at room temperature overnight. The ether was evaporated at 25° under reduced pressure, nearly to dryness, when an exothermic reaction with darkening of colour took place. The gummy

residue was treated with ether and benzene several times. The insoluble residue yielded ammonium chloride (1.4 g.). The combined benzene and ether extracts were concentrated and chromatographed on alumina. Elution with petroleum-ether mixture (2:1) yielded azobenzene (3.0 g., 50%), m.p., mixed m.p. 68°. Subsequent elution with methanol gave a polymeric, blue amorphous powder (2 g.) with no distinct melting point.

ν max (KBr) 1730, 1630, 1600, 1520, 1500 cm^{-1}.

In another experiment the reaction mixture was stirred for four days at room temperature with the same result as described above. However, when the reaction was carried out in methylene chloride no exothermic reaction occurred and only 25% of azobenzene was isolated.

(ii) Hydrazobenzene.

Chloramine in ether (200 ml. of 0.1M solution, 0.02 mole) at -10° was added to hydrazobenzene (4g., 0.021 mole). The reaction mixture was treated as above and gave only azobenzene (3.5g., 90%) m.p. and mixed m.p. 68°. No exothermic reaction took place. Ammonium chloride (1.1 g.) was isolated.

(iii) Phenylhydrazine.

Freshly distilled phenylhydrazine (10 g., 0.09 mole) and ethereal chloramine (500 ml. of 0.28M solution, 0.14 mole) were reacted as before and yielded azobenzene (3.3 g., 20%), confirmed by mixed m.p. and u.v. spectra.

Substituted Anilines.-

(i) p-Toluidine.

Chloramine in ether (200 ml. of 0.25M solution, 0.05 mole)

at -10° was added to p-toluidine (3.6 g., 0.03 mole), and the reaction mixture stirred at room temperature for 12 hr. The solvent was removed under reduced pressure at 25°, soon afterwards an exothermic reaction occurred. The residue was treated with benzene and the mixture filtered, the insoluble residue yielded ammonium chloride (1.6 g.). The benzene filtrate was concentrated and chromatographed on alumina. The first yellow band eluted with petroleum-benzene mixture (7:1) yielded trans-4,4'-dimethylazobenzene (2.1 g., 30%) m.p. 144°, (lit.[123] 145°)

ν max (Nujol) 1600, 1510, 1465, 1380 cm^{-1}.

λ max (EtOH) 207, 236, 333 mμ;

ε max (EtOH) 16,000, 21,000, 37,000

The second red band eluted with petroleum-benzene(1:1) mixture gave cis- 4,4'-dimethylazobenzene (1.05 g., 15%) m.p. 100° (lit.[123] 105°).

ν max (Nujol) 1620, 1610, 1590, 1570, 1520, 1465, 1380 cm^{-1}.

λ max (EtOH) 207, 292, 331 mμ;

ε max. 10,000, 8,000, 9,000.

(ii) p-Chloroaniline.

Ethereal chloramine (0.05 mole) and p-chloroaniline (3.2 g., 0.025 mole) were reacted as above. After the exothermic reaction, the residue was extracted with chloroform. The chloroform insoluble residue gave ammonium chloride, the filtrate was chromatographed on alumina. The first fraction eluted with petroleum-benzene mixture (3:1) gave trans- 4,4'—dichloroazobenzene (1.26 g., 20%) m.p. 187° (lit.[126] 188°).

ν max (Nujol) 1595, 1580, 1485, 1470, 1380 cm^{-1}.

λ max (EtOH) 206, 235, 325 mμ;

ε max 17,000, 23,000, 42,000.

The second fraction eluted with petroleum-benzene mixture (1:1) yielded cis- 4,4'-dichloroazobenzene (1.26 g., 20%) m.p. 129-30°. (Found: C, 58.59, 57.79; H, 3.86, 3.77; N, 10.24, 9.71. $C_{12}H_8N_2Cl_2$ requires C, 57.42; H, 3.21; N, 11.16%).

ν max (Nujol) 1595, 1570, 1515, 1495, 1465, 1380 cm^{-1}.

λ max (EtOH) 211, 292 mμ;

ε max 22,000, 15,000.

(iii) p-Amino N, N-dimethylaniline.

Ethereal chloramine (0.14 mole) and p-amino N, N-dimethylaniline (0.07 mole) were reacted and treated as above. The first orange band eluted with petroleum-ether mixture (3:2) gave trans- 4, 4'-di-(dimethylamino) azobenzene (10%) m.p. 273°, (lit.[127] 273°). (Found: C, 71.66; H, 7.88; N, 21.30. Calc. for $C_{16}H_{20}N_4$ C, 71.70; H, 7.52; N, 20.91%).

ν max (Nujol) 1600, 1560, 1515, 1465, 1330 cm^{-1}.

λ max (EtOH) 208, 255, 325 mμ;

ε max 3,000, 2,000, 830.

The second red band after elution with ether yielded cis-4,4'-di-(dimethylamino)azobenzene (12%) m.p. 220°. (Found: C, 73.95, 70.48; H, 7.57, 7.02; N, 17.50, 18.31. $C_{16}H_{20}N_4$ requires C, 71.70; H, 7.52; N, 20.91%).

ν max (Nujol) 1600, 1560, 1515, 1465, 1370 cm^{-1}.

λ max (EtOH) 206, 257, 333 mμ;

ε max 2,000, 1,000, 750.

The third purple band eluted with methanol gave a dark blue, polymeric solid with no distinct m.p.

ν max (Nujol) 1610, 1520, 1470, 1380 cm^{-1}.

λ max (EtOH) 210, 267 mμ.

(iv) 2-Aminobiphenyl.

2-Aminobiphenyl was reacted with chloramine as above. The t.l.c. of the reaction mixture gave two spots and a long streak, neither of these spots, nor the streak, were comparable to carbazole run under the same conditions. The mixture was chromatographed on an alumina column. The first orange yellow band was eluted with petroleum and gave trans- 2,2' azobiphenyl (10%) m.p. 144° (lit.[128] 144.5°). The second crimson red band eluted with ether yielded cis- 2,2' azobiphenyl (10%) m.p. 42-43°. (Found: C, 86.10; H, 5.75; N, 8.42. $C_{24}H_{18}N_2$ requires C, 86.30; H, 5.43; N, 8.39%).

(v) p-Ethoxyaniline.

Chloramine in ether (500 ml. of 0.1M solution, 0.05 mole) at -10° was added to p-ethoxyaniline (7.3 g., 0.05 mole) and treated as above. After the exothermic reaction, the residue was treated with water to remove ammonium chloride. The insoluble residue was dissolved in methanol and chromatographed on alumina. The yellow band eluted with petroleum gave trans 4, 4' - diethoxyazobenzene (4.7 g., 33%) m.p. 157-59° (lit.[120] 160°).

λ max (EtOH) 205, 241, 356 mμ;

ε max 9,000, 7,000, 17,000.

No cis- isomer was detected on the column.

(vi) Benzylamine.

Chloramine in ether (500 ml. of 0.28M solution, 0.14 mole) was added to benzylamine (10 g., 0.09 mole). The reaction mixture was stirred and after 0.5 hr. a white precipitate appeared. The stirring was continued at room temperature for 12 hr. The white residue of ammonium chloride (2.5 g.) was filtered off and the filtrate was con-

centrated under reduced pressure. The residue was treated with petroleum and yielded benzylamine hydrochloride (30%) m.p. 254°. (Found: C, 57.98; H, 7.20; N, 9.80. Calc. for $C_7H_{10}NCl$ C, 58.79; H, 7.05; N, 9.80%).

The petroleum filtrate yielded benzaldehyde (30%) isolated as its 2, 4-dinitrophenylhydrazone, m.p. and mixed m.p. 235°.

(vii) Attempted Oxidation.

p-Nitroaniline, 2, 4, 6 tribromoaniline, benzamide, acetanilide, 2-aminopyridine, t-butylamine when treated with ethereal chloramine solution as described above were recovered unchanged (95%).

Oxidation of Alcohols.-

(i) Benzyl alcohol.

A mixture of benzyl alcohol (5.4 g., 0.05 mole) and ethereal chloramine (500 ml. of 0.1M solution, 0.06 mole) was stirred overnight at room temperature. After removal of the solvent under reduced pressure, an exothermic reaction occurred. The residue was extracted with benzene, the ammonium chloride (1.5 g.) filtered off and the filtrate concentrated to yield benzaldehyde (4 g., 74%), identified as its 2, 4-dinitrophenylhydrazone m.p. 235°.

(ii) Diphenylmethanol.

Diphenylmethanol (4.6 g., 0.02 mole) and ethereal chloramine (500 ml. of 0.1M solution, 0.04 mole) when treated in a like manner yielded ammonium chloride (1.2 g.) and benzophenone (4 g., 87%) m.p. 48°, 2, 4-dinitrophenylhydrazone m.p. 238°, also confirmed by mixed m.p. and infra red spectra.

(iii) Cyclohexanol.

Ethereal chloramine (0.07 mole) and cyclohexanol (0.05 mole) were mixed and treated as above. Ammonium chloride (1 g.) and a yellowish oil (4.12 g.) were isolated. This oil was the mixture of cyclohexanol and cyclohexanone shown by its infra red spectrum.

ν max (liquid) 3400 to 3300 (OH), 2940, 2860 (CH_2), 1720 to 1710 (C=0), 1450 cm^{-1}

ν max (liquid) cyclohexanol 3400 to 3300, 2940, 2860 (CH_2) 1450 cm^{-1}.

(iv) Attempted oxidation.

Cholesterol and allyl alconol when treated with chloramine as above did not react and in both cases (90%) unreacted starting materials were recovered, checked by i.r. spectra.

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